VOLUME 98 • AUGUST 1959 • NUMBER 2

JOURNAL OF DISEASES OF CHILDREN

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Lamellar Exfoliation of the Newborn, or Ichthyosis Congenita
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Disseminated Histoplasmosis Treated with Amphotericin B
Ruth M. Heyn and Samuel T. Giammona

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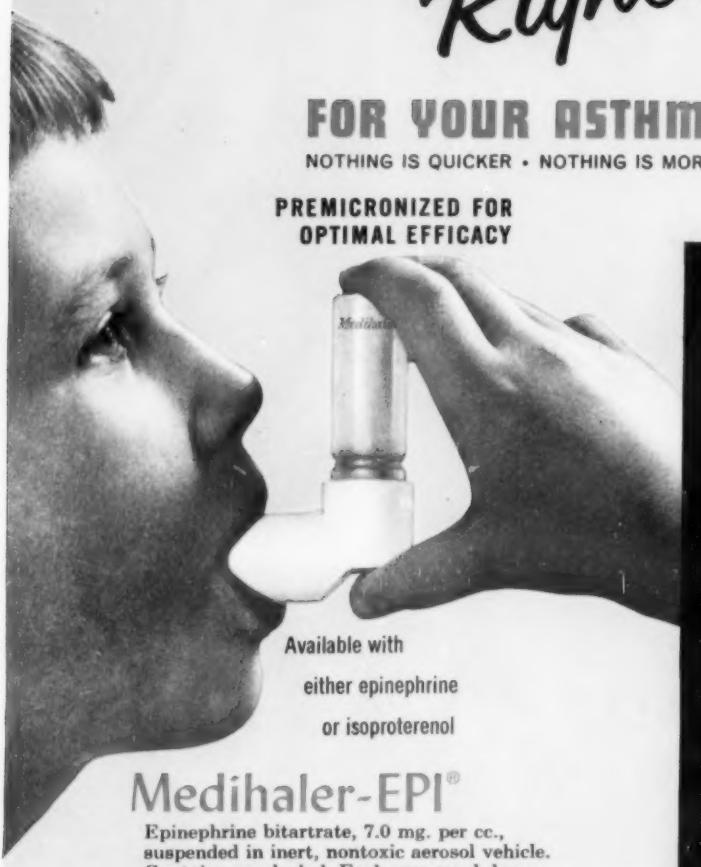

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Journal of Diseases of Children

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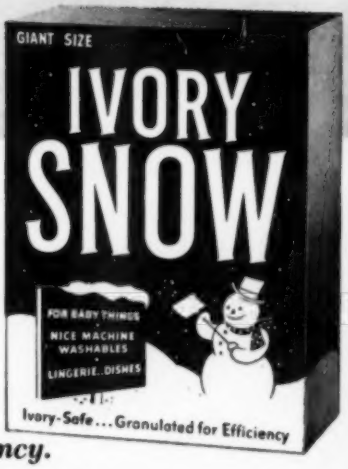

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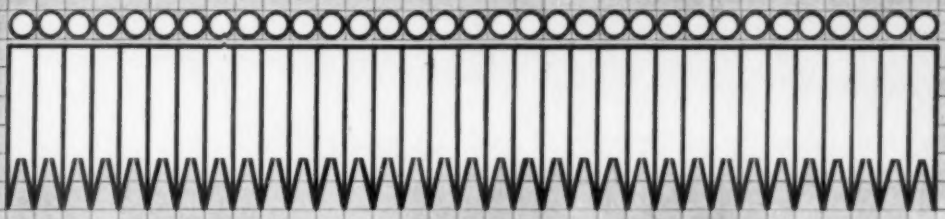

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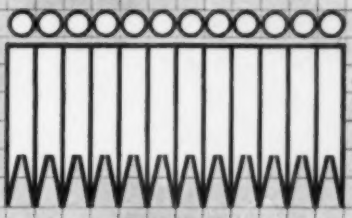

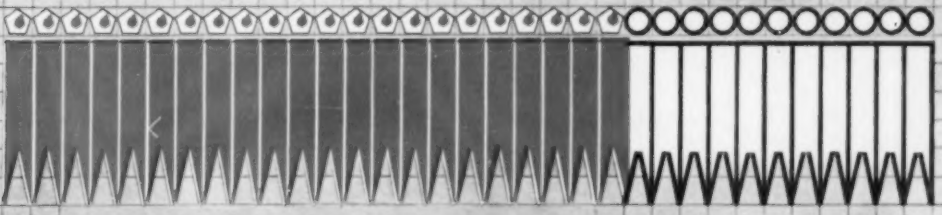

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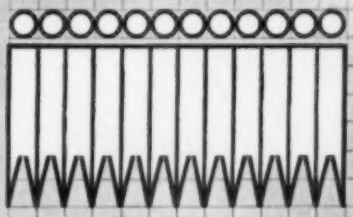

1. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.
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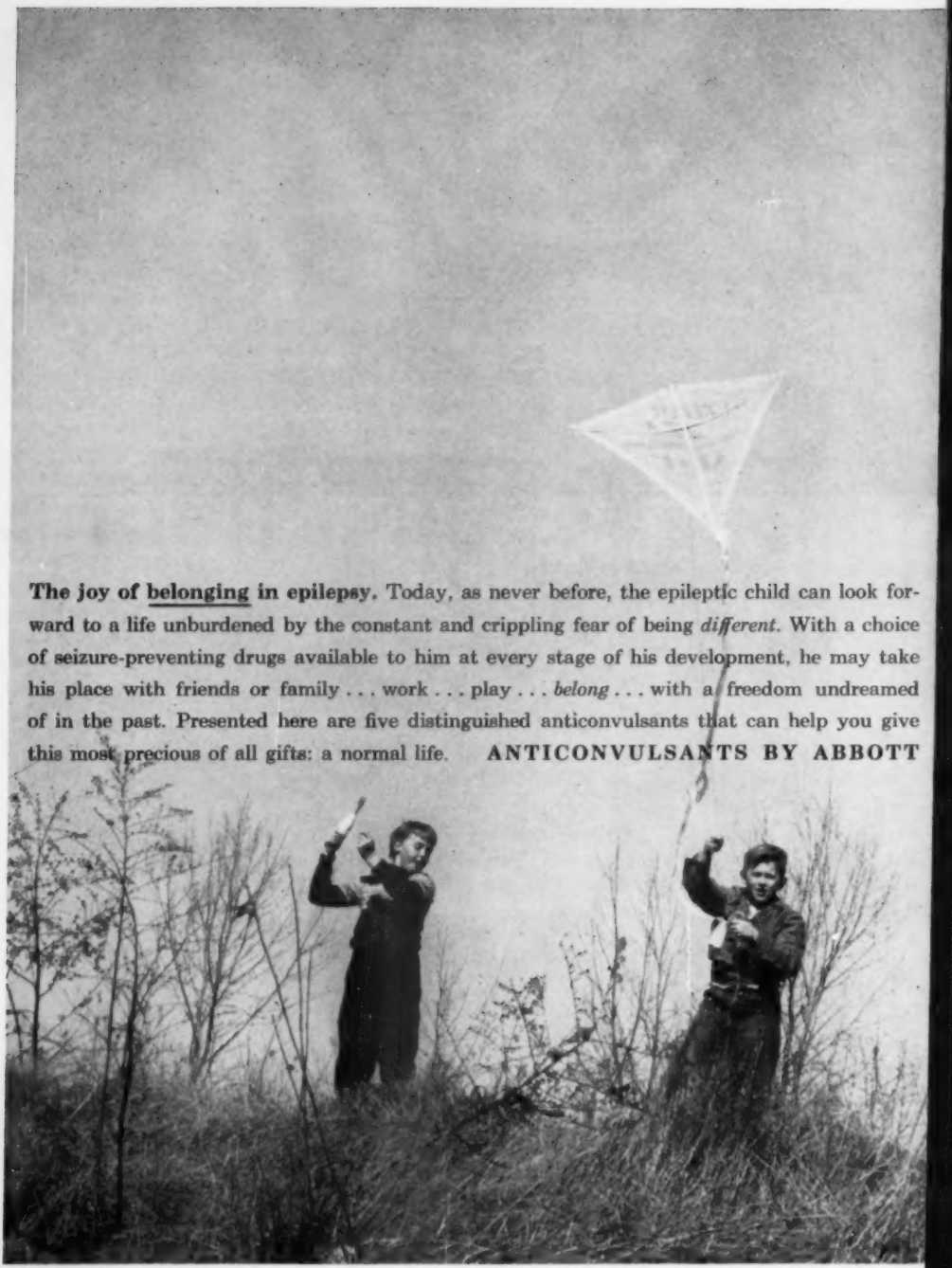

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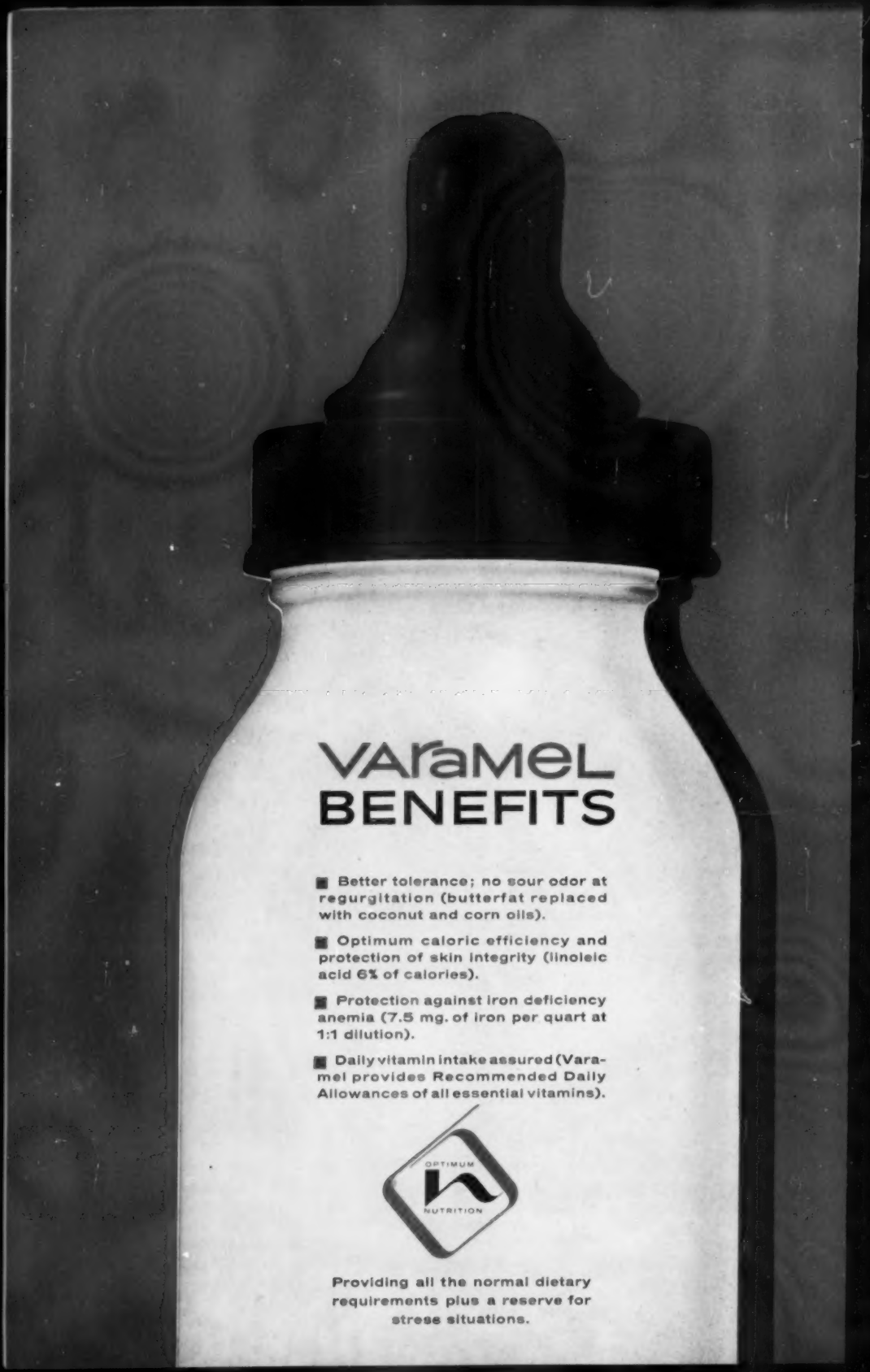
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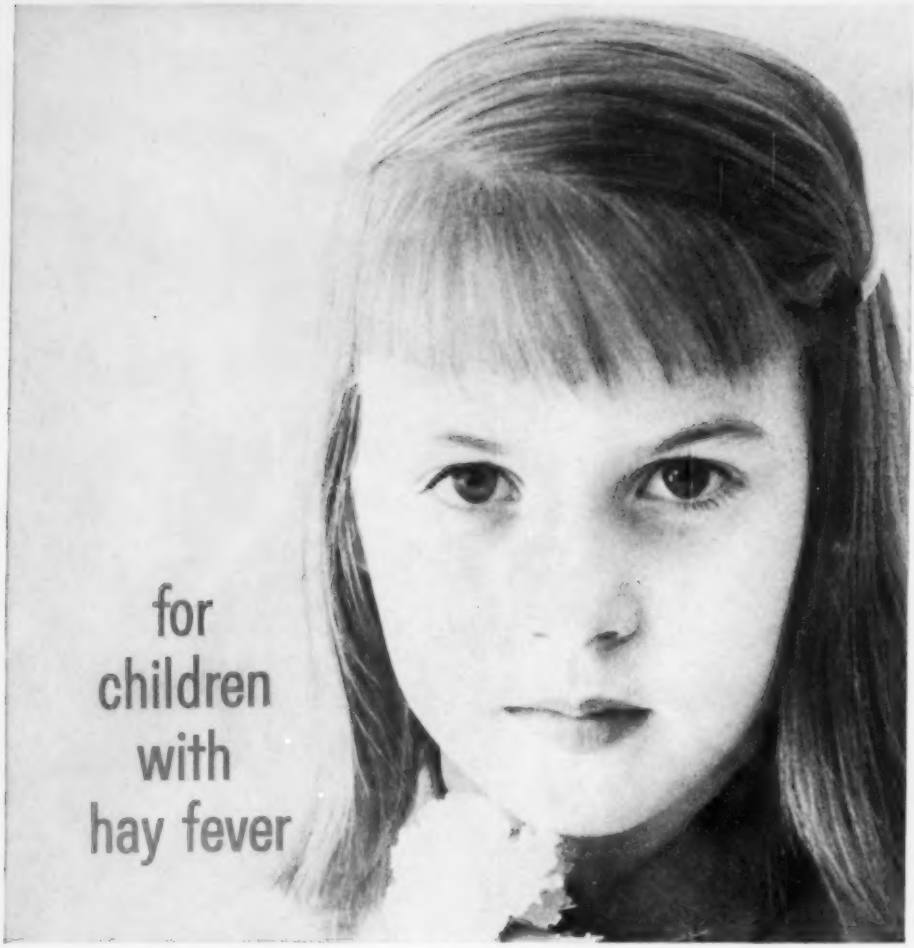

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The Distribution of Poliomyelitis and ECHO Viruses in a Children's Institution

CARLO MOSCOVICI, Ph.D., Denver; ADRIANO GINEVRI, M.D., Rome, and C. HENRY KEMPE, M.D., Denver

The ECHO group of viruses has been continuously under extensive study by many workers. Until now, all of these strains have been isolated from cases of illness, including aseptic meningitis, nonparalytic poliomyelitis, diarrhea, summer rash, etc.,[2-13] respiratory illness,[15] or from healthy children.[14] Twenty-four antigenic prototypes have been recognized [1] to date.

In the course of a poliomyelitis survey in Rome in 1956, we were interested in a community of healthy children under 2 years of age. This study was performed because very little endemiological work on enteric infections had been recorded in Italy, and because it seemed desirable to develop data on the enteric viral flora among apparently healthy Italian children. These studies were done at the orphanage of the Municipality of Rome, which accepts an average of 500 children. The present study, extending previously reported data,[16,17] reports the isolation of 129 strains of tissue culture cytopathogenic agents from rectal-swab specimens collected at monthly intervals from a total of 416 healthy children over a period of eight months from January to August, 1956. We also surveyed for one year a group of 52 newborn babies in a nursery located in the same building. From this group, 51 cytopathogenic agents were isolated in tissue culture.

Submitted for publication Jan. 23, 1959.

University of Colorado Medical Center (Drs. Moscovici and Kempe); Istituto Superiore di Sanità (Dr. Ginevri).

This study was supported in part by a grant from USPH (E-1632), Ross Laboratories, and Chas. Pfizer & Company, Inc.

The studies reported in this paper have been carried out in part at the Istituto Superiore di Sanità, Rome, Italy, and in part at the Department of Pediatrics, University of Colorado Medical Center, Denver.

Procedure and Methods of Study

Rectal-swab specimens were obtained during monthly visits to the various departments in the orphanage. Almost all of the children were under 2 years of age; each dormitory of the orphanage contained around 30 infants. The technique involved in collection of the study material has been previously described.[16] Trypsinized Cynomolgus or Rhesus monkey kidney cells grown in stationary tubes were the only tissue cultures used for primary isolation. The outgrowth medium was that described by Ramos-Alvarez and Sabin,[18] and the same medium for maintenance was used.

Viruses.—All the strains isolated were screened against 3 polio antisera, 19 ECHO antisera, Coxsackie A9 antiserum, and the 5 Coxsackie B antisera. Some of the virus strains have been passed in HeLa cells, and all but the polio inoculated in newborn and adult mice after the positive tissue culture fluids had been passed four to five times. The hemagglutinin properties of each isolated ECHO-prototype was studied, using chicken and human group-O red blood cells at different temperatures in order to facilitate classification.[19]

Sera.—Specific antisera (rabbit or monkey) for polio, ECHO, and Coxsackie were used for the

TABLE 1.—*Isolation of Polio Virus and Other Cytopathogenic Agents from Rectal Swabs of 416 Children Living in an Orphanage in 1956*

Age By Months	No. Subjects Examined	Polio Virus Isolated (% Children Studied)	Nonpolio Viruses Isolated (% Children Studied)
0-6	198	9.09	26.2
6-12	155	14.83	9.6
12-18	60	25	10
18-24	2	--	--
24-30	1	--	--
0-30	416	13.46	17.54

neutralization tests. The adenoviruses were typed against sera prepared by us in rabbits, utilizing HeLa cells for identification.

Neutralization Tests.—The classic technique using final 100 TCD_{50}/0.2 ml. of virus and calculation of the end-point using the Reed and Muench method was used.[19] Only the human sera were heated at 56 C for a half-hour.

Results

Table 1 shows the results obtained in virus isolation from the group of 416 children examined. A higher percentage of nonpolio viruses was found in the group of children aged 0 to 6 months; the percentage decreased with increasing age.

Table 2 describes the distribution of the various types of enteric strains isolated in the group of children examined.

The predominance of the ECHO 15 strains (55.2%) is of considerable interest, as is the fact that Polio Type 2 was the sole polio type isolated during the entire survey in this group of children.

TABLE 2.—*Different Types of Viruses Eliminated from Stools of 416 Children Living in an Orphanage in 1956*

Virus Recovered	Strains Total	% Children	Serologic Strains Type	No.	%
Poliomyelitis	56	13.4	2	56	100.0
Adenoviruses	6	1.4	1	1	16.2
			2	2	33.3
			3	2	33.3
			6	1	16.2
ECHO	67	16.1	9	10	14.9
			11	9	13.4
			12	6	9.0
			13	1	1.5
			14	4	6.0
			15	37	55.2

Results from the newborn nursery of the orphanage are reported in Table 3. Fifty-one cytopathogenic agents were isolated from a total of fifty-two infants. Only 15 of these infants were observed regularly each month for a whole year, since many of them were discharged for adoption or returned to their mothers during this study. Eight polio viruses were isolated. Polio Type 2 occurred four times in January and once in May. Polio Type 3 occurred in three of these five infants subsequently in December (Nos. 150, 152, 170). No Polio Type 3 occurred in any child who did not previously have Polio Type 2 excretion.

The enterovirus pattern in the newborn nursery study is shown in Table 4. Besides Polio Types 2 and 3, five different types of ECHO are represented and three different types of adenoviruses. Evident here also is the prevalence of ECHO Type 15 (32.4%). Polio Type 2 was not isolated from the infants admitted subsequent to the January sampling, whereas ECHO viruses were isolated from almost all of the same new admissions.

Antibody studies with children's sera (Table 5) show a high incidence of protection among the 26 Polio 2 excretors, while no antibody could be found in this group against Type 3, and only 11.5% against Type 1. Unfortunately, it was not possible to screen more than 12 sera among the ECHO carriers. Even if these results have no statistical significance, of these 12 children 5 did show presence of antibody against ECHO 15.

Comment

It is well known that a diverse group of ECHO viruses are more commonly found among healthy persons than during epidemics, where, in general, only one antigenic type is represented.[14,20]

The age distribution of the enteric flora shows also a higher percentage of ECHO strains among the 0-6-month group (26.2% in the largest group studied), whereas the polio percentage is lower (9.09%) in the

TABLE 3.—*Distribution of Viral Flora in the Newborn Nursery*

Patient No.	Age Mo/ Days	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
141 *	8/0	APC 6					Echo 15	Echo 15	Echo ?				
142 *	0/9												
143 *	0/29							Echo 14					
144 *	1/4												Echo 12
145 *	1/1	Echo 15											
146 *	7/5							Echo 14					
147 *	3/21						Echo 15		Echo 9				
148	3/26												
149 *	5/2												Echo 14
150 *	7/3					Polio 2							Polio 3
151	7/3							Echo 15					Echo 12
152 *	7/14	Polio 2						Echo ?					Polio 3
153	8/18												
158	0/17							Echo 15					
159	0/17												
160 *	3/6								Echo 9				
161	11/21												
162	11/21												
163	11/23												
164	11/4												
165	11/21												
170 *	8/3	Polio 2						Echo 14					Polio 3
171	9/2												
172	16/14												
173	3/16									Echo 9	Echo 11		
174 *	3/27	Polio 2								Echo 11			Echo 12]
175	4/27												
176 *	8/17	Polio 2						Echo 14	Echo 9				
307	0/21						Echo 15						
308	1/11												
309	1/17												
310	1/25												
311 *	1/25					APC 3	Echo 15				Echo 11		Echo 11
312	1/11						Echo 15	Echo 14			Echo 12		
314	0/14												
349	0/9										Echo 11		
350	0/9												
351	0/19												
352	0/23						Echo 15						Echo 12]
353	1/7												
381	0/27								Echo 9				
382	0/28										Echo 11		
383	5/13							Echo 15					
440	1/5												
441	3/12								APC 1				
442	1/20										Echo 11		
443	6/20							Echo 9					
444	0/11												
445	1/20										Echo ?		
446	1/3												
453	—											Echo 12	
169	1/21							Echo 15					

* These are the children followed for an entire year.

same group and becomes higher with increased age (Table 1).

In the newborn nursery study, the difference between ECHO viruses and polioviruses is even more striking; here we found 71.1% of ECHO strains against the 15.3% for polioviruses and 5.7% for adenoviruses.

During 8 months' study of 416 children, and 12 months' study of 52 newborn infants, Polio 2 was recovered exclusive of other polio strains in the older children. In the nursery, Polio 2 was recovered in 5 of the 8 children excreting poliovirus; the other 3 yielded Polio 3. During the time of the study several cases of Type 1 paralytic and

TABLE 4.—*Incidence of Different Viruses Among Cytopathogenic Agents Isolated from Rectal Swabs of Fifty-Two Infants in the Newborn Nursery*

Virus Recovered	No. Strains	% Total Strains	Serologic Type	No. Strains	%
Poliomyelitis	8	15.9	2	5	62.5
			3	3	37.5
Adenoviruses	3	5.8	1	1	33.3
			3	1	33.3
			6	1	33.3
ECHO	37	72.5	9	6	16.2
			11	7	18.9
			12	6	16.2
			14	6	16.2
			15	12	32.4
Unidentified	3	5.8		3	
Totals	51	100%		51	

TABLE 5.—*Neutralizing Antibodies in Children's Sera Collected After Ten to Forty Days from Date of Virus Isolation*

No. of Sera Tested	Viruses Recovered	Virus Used in Neutralization Test	No. of Children c Significant Titer/0.2 Ml. Antibody (128 or >)	% Total
26	Polio 2	Polio 1	3	11.5
		Polio 2	26	100.0
		Polio 3	--	--
12	Includes	ECHO 9	3 *	25.0
	Polio 2,	11	2	16.6
	APC 6,	14	—	—
	ECHO8	15	5	41.6

* Titer for ECHO antibodies ranges from 8 to 64.

nonparalytic poliomyelitis occurred in Rome (but not in the institution).

The prevalence of ECHO 15 is evident in both groups. In the older children 37 ECHO 15 strains (55.2%) are present among 67 ECHO isolations; in the newborns 12 ECHO 15 strains (32.4%) are found among 37 ECHO isolations. The significance of these findings in relation to disease is as yet unknown. To date ECHO 15 has not as yet been found implicated as a pathogenic agent.[1] Evidently ECHO 15 was widely distributed around the whole orphanage at this time.

Summary

The incidence of enterovirus infections has been studied in 416 apparently healthy children under 2 years of age during the period January-August, 1956, in Rome, and simultaneously for a whole year in a newborn nursery of the same institution.

Polio and ECHO viruses were commonest representatives of the enterovirus group found; a few adenoviruses were recovered. Only Type 2 of poliovirus was isolated from the older children (13.4%), as well as ECHO (16.1%) and 6 adenoviruses (1.4%). Six different types of ECHO are represented with a predominance of ECHO Type 15 (55.2%).

Polio Type 2 and Type 3, ECHO, and adenoviruses were isolated in the newborn nursery. Here, also, ECHO Type 15 was the predominant strain (32.4%) among the ECHO group. No Polio Type 3 occurred in any child who did not previously have Polio Type 2 excretion.

4200 E. 9th Ave. (20).

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Residual Encephalopathy Following Roseola Infantum

RICHARD C. BURNSTINE, M.D., North Kingston, R. I., and RICHMOND S. PAINE, M.D., Boston

Introduction

Roseola infantum, first described by Zahorsky [1] in 1913, is generally considered a benign disease; indeed, Kempe [2] noted there are no reported fatalities. Serious sequelae are usually stated to be virtually nonexistent. However, the possibility has been suggested in a comprehensive view of the subject,[3] that some of the sudden deaths in infancy may be caused by roseola. No clear instances of this have been reported, no doubt owing to the difficulties of making a positive identification of the disease in the preeruptive stage and the inability to isolate the virus in tissue culture.

Roseola infantum is the commonest exanthem under the age of 2 years, and infection is perhaps almost universal before the age of 5 years.[3] The disease is characterized by the relative absence of prefebrile prodromata, an abrupt onset, and a rapid temperature rise. Irritibility and listlessness are variable; the patient is usually active, alert, and appears well. The temperature is constantly or intermittently elevated for three to five days, subsiding by lysis or crisis coincident with or preceding the appearance of a characteristic maculopapular rash, primarily on the neck and trunk. The rash may be quite fleeting or may not be detected at all. Early in the course of the disease there is a slight leukocytosis, followed by a leukopenia and relative lymphocytosis. The cerebrospinal fluid is usually reported as being within normal limits.

Convulsions are well recognized as a common occurrence in this disease, the reported incidence varying from 0.6% to 50%,[3,4] depending on whether reported from private practice or from large hospitals handling primarily referral cases. The exact incidence of seizures occurring with roseola is thus difficult to estimate; this difficulty is further compounded by the confusion of the rash with other exanthemata and drug eruptions.

In a review of febrile convulsions, Möller [5] noted they occurred in 1.5% of all the patients under the age of 16 years admitted to his hospital; infectious diseases were not admitted. Roseola accounted for 34 out of 448, or 7.6% of all febrile convulsions. The median age of those having convulsions associated with roseola was 12.5 months, whereas it was 20.8 months in the remainder. Lumbar punctures were performed in 29 of the 34 cases; 6 showing an elevated CSF pressure, 2 with 5, and 1 with 9 cells per cubic millimeter. Subsequent to the roseola, two patients had convulsions associated with fever, and the patient with 9 cells in the cerebrospinal fluid developed grand mal seizures, in the absence of a family history, electroencephalographic abnormality, or detectable cerebral lesion. Möller notes that some of the seizures ascribed to pharyngitis—79.9% of all febrile seizures—may have been caused by roseola. He suggests that there is a specific cerebral disturbance other than the fever itself, because high fevers in other conditions, such as pyelitis and bronchopneumonia, in his series, were not associated with such a high incidence of convulsions. He also postulates that roseola may have a persisting cerebral lesion.

Scattered reports of instances of transient or permanent neurologic sequelae of roseola infantum have appeared in the literature. Berenberg et al.[3] reported two cases of hemiparesis lasting two and five days re-

Submitted for publication Jan. 29, 1959.

From the Department of Pediatrics, Harvard Medical School, and the Department of Medicine, The Children's Medical Center, Boston.

spectively, with no apparent residual. Holliday [6] reported five cases of "pre-eruptive neurological complications" of roseola. His first case cannot be included as unquestionably related to roseola, as the neurological signs appeared six days prior to the rash. His other four cases demonstrated meningismus and/or meningoencephalitis during the preeruptive febrile period. Lumbar punctures in two of the four demonstrated slight pleocytosis. Recovery was uncomplicated in three of the four. One case developed petit mal seizures six months later; the relationship of the latter to the roseola is not clear. Windorfer,[7] in his series of 117 cases of roseola, reported 4 cases of hemiparesis; 2 lasted for one day, and 1 for two days. The fourth case lasted for six weeks. Apparently there were no permanent residua.

Rosenblum [8] reported a 19-month-old white female child who had four convulsions, including one of three and one-quarter hours. A lumbar puncture at this time was not remarkable. The fourth day following the crisis, the characteristic rash of roseola was noted as well as a left hemiplegia, which cleared after seven weeks. Posson [9] reported two cases. The first, a 15-month-old girl, was irritable for three days and then developed a fever of 104.3 F with generalized convulsions for three-quarters of an hour. Four hours later another convulsion occurred with a temperature of 106.2 F, followed by stupor and a right-sided weakness noted the following day; after four hours the classical rash of roseola appeared. The stupor cleared in 10 days. The involvement of face and leg cleared within two months, but weakness was still noted in the hand and arm one year later. Posson's second case was that of an 18-month-old boy with a nine-hour convulsion and a temperature of 105.4 F. He was comatose for several days, and a right hemiplegia followed. The classical rash appeared six hours after discharge. Friedman [10] reported the case of a 9-month-old boy who entered the hospital in coma on the second day of fever and then had a convulsion. Three and a half hours later he had a right-sided convulsion. The cerebrospinal fluid contained 5 white blood cells per cubic millimeter, and the Pandy test was negative. The rash appeared on the fourth day of the illness. On the fifth day, the cerebrospinal fluid contained 25 white blood cells, mainly polymorphonuclears, and 1,100 red cells. Six days after the rash there were 20 white cells, including 1 neutrophil. Eighteen days after the onset of illness the patient showed only residual hemiparesis on the right; no later follow-up data are available. Del Mundo [11] reported a 12-month-old white boy with a six-hour generalized seizure on the second day of illness accompanying a temperature of 104 F. The patient then became comatose and, on the following day, a right hemiparesis was noted. The rash appeared on the fourth day. The residual weakness disappeared within a week. Lumbar puncture on the second day revealed no cells in the spinal fluid, and the Pandy test was negative. Del Mundo's second case had no convulsions or residua, but merely a clouded sensorium with meningismus; no laboratory procedures were performed. Glanzmann [12] mentioned one case of transitory hemiparesis.

Report of Cases

The present paper presents six cases of hemiparesis acquired in association with roseola (Table). Follow-up data are available on five, in all of whom the hemiparesis was permanent. At least three are mentally retarded, and three are epileptic.

CASE 1.—This female child had one febrile convulsion with temperature of 102 F accompanying a respiratory infection at the age of 3 months, but was otherwise well until roseola developed at 7 months. Maximum fever is unknown, but four convulsions lasting about one hour each occurred on the day the rash developed. Seizures began on the right side, but were chiefly left-sided, and the last was followed by left hemiparesis. Seizures were severe and required ether to control them. At age 16 months, 9 months after onset, the child still has a left hemiparesis and is mildly or moderately mentally retarded, performing generally at an 11-12-month level at chronological age 16 months. She continues to have an average of one grand mal seizure monthly, usually accompanying

Summary of Six Cases of Hemiparesis Following Roseola

Case No.	Age at Onset, Mo.	Past History	Family History	Maximum Temp., F	Days Until Rash	Days Until Seizures	Length of Seizures	Anoxia with Seizures
1	7	Febrile convulsions at 3 mo. with temp. of 102 F	Childhood seizures in maternal aunt and uncle	Unknown	Day of convulsion	Just prior to rash	4, 1 hr. each	Probably severe; stopped with ether
2	16	Mild fall one week before roseola	Noncontributory	106	4th day of illness	1 ½ days of fever	Probably over 4 hr.	Unknown
3	12 ½	Mother bled in first 6 mo. of pregnancy; had hyperemesis	Febrile convulsions in cousins	105	3d day of illness	1st day of fever	Unknown	Unknown
4	15	Noncontributory	Noncontributory	104.3	4th day of illness	2d day of fever	16 hr. intermittently	Probable
5	14	Noncontributory	Noncontributory	105	5th day of illness	1st day of fever	12 hr.	Unknown
6	15	Noncontributory	Noncontributory	105.6	3d day of illness	1st day of fever	2 hr., followed by 2 days' coma	Probable

Summary of Six Cases of Hemiparesis Following Roseola (Continued)

Case No.	Type of Seizures	Residual Findings: Months After Roseola	Physical Signs	Mental Status	Further Seizures	Spinal Fluid	Special Tests: EEG	Special Tests: PEG
1	Chiefly, left-sided; last followed by left hemiparesis	9	Left hemiparesis	M. A. 11-12 mo. at C. A. 16 mo.	1 per month, usually febrile	Normal at onset, 16 WBC at 16 mo.	1 mo. after roseola: generalized slowing 9 mo. after roseola: generalized fast and spiking activity	At 16 mo.: mild dilation of left lateral ventricle with shift to right
2	Left side of face; then generalized; followed by left hemiparesis	2	Left hemiparesis (improving)	Not yet clear	None	Normal at 16 mo.	On 2d day: diffuse slowing	Not done
3	Right-sided; right hemiparesis only permanent after 5 more seizures, last at age 2 4/12 yr.	18	Right hemiparesis	M. A. 2 1/12 yr. at C. A. 2 8/12 yr.	Occasional psychomotor variant seizure	Normal at onset	At 1 11/12 yr.: spikes and low voltage fast, mostly on right; at 2 4/12: normal	Not done
4	Right-sided	8 days only	Right hemiparesis	Unknown	Unknown	Normal at onset	At onset: rhythmic high voltage slow waves in left frontal	Not done
5	Left-sided	7 yr.	Left hemiparesis	5-6 yr. level, irregular at C. A. 8 ½ yr.	Generalized tonic-clonic every 1-2 mo.	Unknown	At 8 yr.: bilateral spikes, more prominent on left	Right hemicranium smaller; right lateral ventricle dilated; with shift to right
6	Right-sided; right hemiparesis noted 4 days after convulsion	20	Right hemiparesis with hemianopia	Grossly defective; walks, but no speech	None	Normal at onset and on 2d day	At 3 yr.: diffuse fast activity	At 3 yr.: dilated lateral ventricles, left larger, with shift to left

fever. Spinal fluid examination was normal at onset, but at 16 months showed 16 white blood cells and 2 red blood cells per cubic millimeter, 14 of the white blood cells being mononuclear. Total protein was 14 mg. % and sugar 70 mg. %. The EEG one month after roseola showed general slowing, but at age 16 months there was generalized fast and spiking activity in all leads. Pneumoencephalogram at 16 months (Fig. 1, *a* and *b*) showed mild dilatation of the posterior portion of the left lateral ventricle and a shift of third ventricle to the right, with excess surface air in the subarachnoid space over both cerebral hemispheres and widening of the cerebral sulci. The over-all appearance was of minimal general dilatation of the ventricular system, most marked in the left hemisphere, with mild diminution of total cerebral substance.

CASE 2.—This female child was well and had progressed normally until 16 months, when she developed fever followed by a convulsion after 30 hours. This began on the left side of the face but soon became generalized. Temperature was 106 F, and convulsions probably lasted in excess of four hours, followed by left hemiparesis. Typical roseola rash developed on fourth day of illness, two days after the hemiparesis. Spinal fluid showed 3 red blood cells and 2 mononuclear cells per cubic millimeter; total protein was 15.6 mg. % and sugar 85 mg. %. Bilateral subdural taps were dry. X-rays of the skull were negative. EEG was diffusely slow on the second day of hemiparesis. At

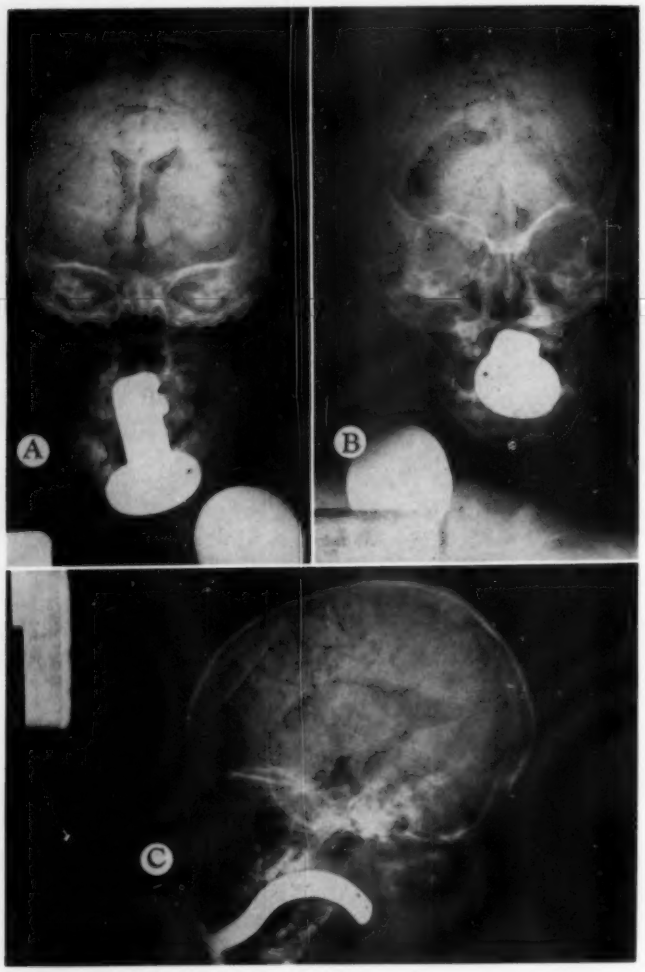

Fig. 1 (Case 1).—Pneumoencephalogram made at age 16 months, 9 months after onset of left hemiparesis at time of roseola at age 7 months. Left and right are reversed in A.

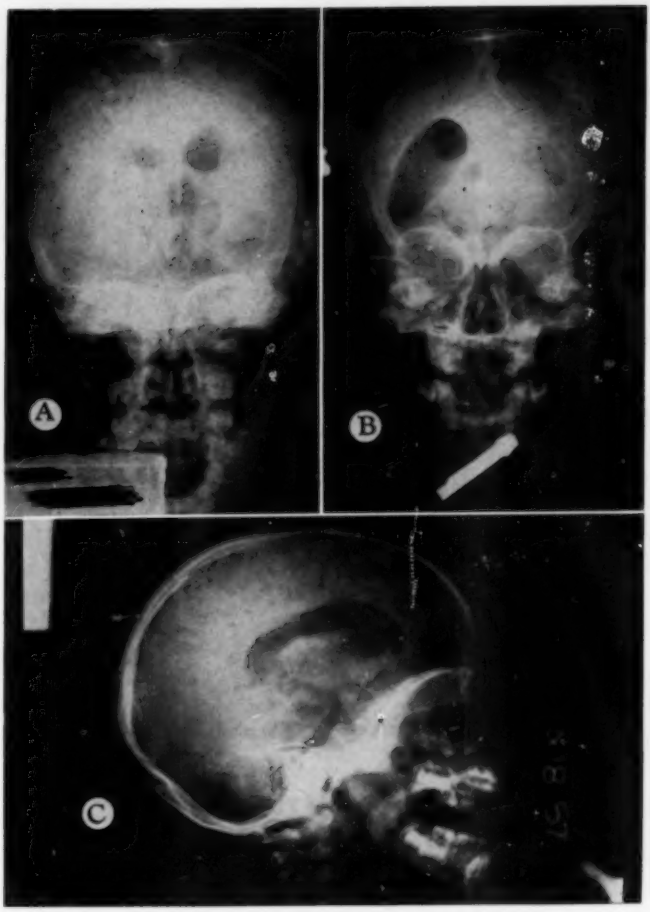

Fig. 2 (Case 6).—Pneumoencephalogram made at age 3 years, 21 months after onset of right hemiparesis at time of roseola at age 15 months. Left and right are reversed in A.

follow-up two months from onset, the hemiparesis was improving but had not disappeared. There had been no further convulsions, but mental status was not yet clear at this time.

Case 3.—Mother had bleeding in first and second trimesters of pregnancy and hyperemesis from the third to the fifth month. The child was well until age 12½ months, when she had right-sided convulsions with fever of 105 F, followed by roseola rash after three days. At 1 7/12 years a second right-sided febrile convulsion lasting two hours occurred, followed by right hemiparesis for about one day. A third attack occurred at 1 8/12 years, a fourth at 1 11/12 years (two hours on right side followed by one day of right hemiparesis), a fifth at 24 months (three-hour, right-sided seizure with high temperature, followed by hemiparesis), and a sixth at 26 months, with temperature 104 F, which was right-sided for five hours, followed by permanent right hemiparesis. The child had sat at 7 months and walked at 1 year. At 2 8/12 years she said only a few words. There was a questionable visual field defect on the right, and slight supranuclear weakness of face and tongue. Her speech was not much more than she had before the first convulsion. EEG was within normal limits. The child was still having episodes of repeated swallowing with an occasional blank look, in spite of medication (phenobarbital, 60 mg. daily). Psychological testing showed 2 1/12-year level at chronological age 2 8/12.

Case 4.—This female child's past history was unremarkable. She sat at 6 months, walked at 10 months, and was well until 15 months, when she had fever of 104.3 F, not relieved by acetylsalicylic acid and followed after one day by persistent predominately right-sided convulsions, not suppressed by phenobarbital 60 mg. every four hours. Right

hemiparesis was noted after 16 hours of intermittent convulsions. The spinal fluid was normal. Another right-sided convulsion occurred two days after hospital admission and four days after onset of illness. At this time, a rash consistent with roseola was noted. EEG showed rhythmic high voltage slowing in left frontal and temporal leads. Right hemiparesis was still present eight days after admission, when child was discharged, but the child was subsequently lost from contact.

CASE 5.—This child was normal until age 14 months, when she had a 12-hour left-sided convulsion with a fever of 105 F, followed by a left hemiparesis. The rash of roseola appeared on the fifth day of illness. The patient is still epileptic, with attacks about every two months in spite of a wide variety of medication. Mental development has been slow, and at 8 years she is attending a special class. Examination shows left hemiplegia with some extrapyramidal involvement, but no sensory loss in the hand. EEG is abnormal, with spikes more prominent in the left hemisphere than right but occurring bilaterally. A pneumoencephalogram shows diminution in size of right hemicranium, slight dilation of right lateral ventricle, and shift toward the right. Psychological testing shows comfortable work at 5- or 6-year level, but some spurts of reasoning ability at 7½-to-8-year level (chronological age 8½ years). The usual "organic" type irregularities are present. The child is taking primidone (Mysoline) with some improvement in seizures, but is harder to manage when she is free from them.

CASE 6.—This male child was well and developed normally until age 15 months. Twenty-four hours after the onset of a febrile illness, he was found comatose by his parents with a temperature of 105.6 F, followed by a right-sided clonic convulsion lasting two hours. He was comatose for two days after this, and on the fourth day after the convulsion a right hemiparesis was noted, as well as the classic eruption of roseola. Examination of the spinal fluid on the day of the convulsion, and again two days later, was negative. Six months after the illness, at the age of 21 months, the child sat up, and twelve months from illness, at 27 months, he walked. He has never developed any speech, however, and seems grossly mentally defective. There is a right hemiparesis and probably a right homonymous hemianopia. Pneumoencephalogram showed general dilation, especially of the left lateral ventricle with shift to the left (Fig. 2, *a*, *b*, *c*).

Comment

Of our six cases (see Table), all except Case 1 had their initial seizure with roseola occurring between the ages of 12 and 16 months. When recorded, the temperature was markedly elevated, and the convulsions usually occurred early in the febrile course of the disease, at least two days before the appearance of the rash (except Case 1). The seizures seemed to be severe, a probable history of anoxia during the seizures being elicited in three of the patients. If adequately described, the seizures were focal in all instances, although they did start as generalized seizures in some patients. Of the five cases that we have been able to follow, one (Case 2) is too near her acute episode to evaluate her residua properly. However, at 2 months, her hemiparesis, though improving, is still present, and her mental status is not yet clear. She has had no further seizures. The other cases still have a persistent hemiparesis, minimal to severe mental retardation, and subsequent seizures in three of the five. Lumbar punctures, when performed, were normal. Electroencephalograms and pneumoencephalograms were variable. The x-rays in Case 6 are noteworthy for the amount of destruction that is evident (Fig. 2).

Case 3 differs from the others in that while the child's first seizure (right-sided, like her subsequent ones) occurred at 12½ months with roseola, no postictal hemiparesis is recorded at that time. She subsequently had five more febrile right-sided seizures, each followed by hemiparesis, which was permanent only after the last of these. We have found such a sequence of events by no means rare in children who have repeated unilateral febrile convulsions, of whatever cause, a situation believed to call for vigorous anticonvulsant medication, given continuously if fever and illness are not evident sufficiently far in advance of the onset of seizures.

The pathological basis of the sequelae in our cases is speculative, and a number of possibilities exist:

1. *Cerebral thrombosis* is suggested by the focal seizures and the precise localization in some, as well as the lack of inflammatory changes in the cerebrospinal fluid. However, this explanation does not seem

adequate in Case 6, in which a diffuse cerebral lesion was demonstrated by pneumoencephalogram.

2. *Anoxia* probably occurred in three cases, and was suggested by Friedman[10] in his case. Asymmetric lesions, including hemiplegia, can almost certainly be based on anoxia, as in accidental suffocation and cardiac arrest during surgical operations; the cerebrospinal fluid findings are consistent with this as well.

3. A *postinfectious encephalitis* with the classic perivascular demyelination seems a less likely etiology, as the complications have appeared prior to the appearance of the rash (which, however, does occur on occasion with the common infectious diseases[6]), are sharply localized, and are accompanied by normal cerebrospinal fluid.

4. The possibility of a *specific encephalitis or encephalomyelitis due to the roseola virus* has been suggested in the papers of Holliday,[6] Rosenblum,[8] Möller,[5] and Posson.[9] Posson noted, "Irritability that accompanies the disease is one of its outstanding features and lasts for two or three days after the rash has disappeared," and suggested a selective action on the brain by the agent causing the exanthem.

5. The *effect of prolonged convulsions* must also be considered, as well as the effect of high temperatures, alone or in combination with other suggested factors. Convulsions continuing for more than one hour are the most striking clinical feature common to all of our cases, and to most of those reported by others. These may conceivably affect the brain directly, as a matter of neuronal exhaustion. More probably, they lead to cerebral damage by anoxia from interference with respirations or by ischemia from vascular spasm or thrombosis. The adverse effect of these factors is increased by the enhanced oxygen demand of the brain associated with the high fever and seizure discharges.

6. A *single and irreversible original lesion* of vascular or other nature might cause both the convulsion and the "residual" encephalopathy so readily attributable to it.

Preexisting cerebral abnormality may have been a factor in Cases 1 and 3. There was a family history of childhood convulsions in both instances. Case 1 had had previous febrile convulsions, and the severe one occurring with roseola may have been only another example of these. Case 3 had a history of maternal bleeding in pregnancy. The child had no hemiparesis with the roseola at 12½ months, but five subsequent febrile convulsions were followed by postictal hemiparesis, which was permanent after the last one at age 28 months. Children with past histories suggesting brain abnormality or with past or family histories of convulsions may be especially subject to encephalopathy in association with roseola.

While all of the cases presented were clinically typical of roseola, it is possible that viral isolation studies, had they been done, might have identified other viral exanthemata, such as those reported with ECHO and Coxsackie virus infections.

Treatment in cases of the type discussed would appear to be largely limited to attempts to prevent or to cut short the convulsions. There may be some basis for administering acetylsalicylic acid and phenobarbital in combination to any child under the age of 2 years with an unexplained high fever, especially if roseola is suspected. Parenthetically, it might be noted that this prophylactic approach may be least satisfactory when we would like to see it used most, namely, in roseola with sudden onset of high fever, if indeed the sudden rise factor does play a major role in the causation of febrile convulsions. However, in reviewing our cases and the cases in the literature, it has become apparent that there is one factor which is common to almost all of them: prolonged convulsions. If these convulsions are a result of thrombosis, anoxia, or an encephalitis, stopping them would not necessarily change the prognosis for the patient. If the hemiparesis results from anoxia, vasospasm, or thrombosis associated with prolonged convulsions, then the need for vigorous treatment of the convulsions

cannot be overemphasized. Febrile convulsions, no matter what their cause, should be treated as effectively and as promptly as possible. (Case 2 was seen by one of us [RCB] after she had been convulsing almost continuously for four hours, and had been given only 60 mg. of pentobarbital (Nembutal) during this time. She subsequently responded promptly to more adequate anticonvulsant measures.)

Summary and Conclusions

Roseola infantum is not always a disease of benign prognosis, and six cases of persistent neurologic complications have been presented. All have residua, including hemiparesis, and in addition, at least three are mentally retarded and three, epileptic. It is felt that the sequelae are related to prolonged seizures occurring during the preeruptive stage of roseola. The incidence of this complication is uncertain. The total reported cases with permanent sequelae now number nine. The exact etiology of these convulsions and of the residual encephalopathy is unclear, and several theories have been discussed.

Possible treatment seems limited to stopping or to preventing the associated convulsions; the need for vigorous therapy of any febrile seizure is emphasized. Acetylsalicylic acid and phenobarbital prophylaxis may be considered in children under the age of 24 months with unexplained high fever, especially if roseola is suspected.

Grateful acknowledgment is due Dr. Merritt B. Lowe, of Greenfield, Mass., who referred Cases 1 and 5 and supplied details of their initial illnesses; and to Dr. Randolph K. Byers for his advice in preparation of this paper.

Potowomut Rd. (Dr. Burnstine).

300 Longwood Ave. (15) (Dr. Paine).

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Ectopic Ureteral Orifice

A Report Based on Seventeen Cases

AURELIO C. USON, M.D., and J. TIMOTHY DONOVAN, M.D., New York

An ectopic ureteral orifice, i. e., the location of one or more ureteral openings in a position outside the bladder, while infrequent, is no longer regarded as a medical curiosity or as a rare finding. Furthermore, the poor hygiene and subsequent mental anguish over the "wetness" caused by this anomaly can usually be remedied if the correct diagnosis is made and competent treatment carried out. On the other hand, if the malformation is overlooked, incompletely evaluated, or improperly treated, poor or discouraging results will be obtained. For these reasons, familiarity with the varied clinical pictures observed in patients with this anomaly and with the basic embryological deviations responsible for it, is of importance to both the pediatrician and the urologist in order to enable either of them to suspect the malformation promptly, to interpret the various clinical findings correctly, to outline a thorough clinical evaluation, and to select the best method of treatment in any given case of ectopic ureteral opening. Familiarity is also necessary with the various special techniques employed in modern urological diagnosis and treatment. Bearing this in mind, we have reviewed the available medical literature on the subject, as well as the clinical records of 17 patients with ectopic ureteral openings treated at the Squier Urological Clinic and the Babies Hospital from 1933 through 1956. The pertinent clinical data obtained from the records of these 17 cases are presented in Tables 1, 2, 3, 4, 5, 6, and 7, and form the basis of this report.

Submitted for publication Dec. 12, 1958.

Squier Urological Clinic, Columbia-Presbyterian Medical Center.

Comment

Sex and Age of the Patients.—As shown in Table 1, of the 17 patients 15 were female, ranging in age from 3 weeks to 23 years. The two males, Cases 8 and 17, were 41 and 22 years of age, respectively, when the anomaly was discovered. These two patients died; Case 8 of disseminated carcinoma of the anomalous renal pelvis and Case 17 of renal failure as a result of the malformation. In both, the ureteral ectopia was not recognized clinically, but was discovered during postmortem examination. Of the 15 females, Case 9 was the only adult. This patient was 23 years of age when the ectopic ureteral opening was found but she had been complaining of "urinary incontinence" off and on all her life. In this case, hymenectomy for an incompletely perforated hymen was performed at age 23 and only then was the ectopic ureteral orifice visualized and adequate treatment instituted.

Complaints and Findings.—As shown in Table 3, pyuria, incontinence, and fever were the symptoms and findings most commonly reported. Neither the 2 males nor 7 of the 15 females complained of incontinence. Therefore, the absence of incontinence did not necessarily exclude the possibility of an ectopic ureteral orifice in the urethra, or even in the vagina. The results of the various laboratory studies were unremarkable except for the high blood urea retention and acidosis in Case 17, and the present of slight pyuria (2-10 leukocytes in each high-power microscopic field) in nine patients, four of whom (Cases 1, 9, 12, and 13) also had leukocytosis. These latter four had fever and acute pyelonephritis

TABLE 1.—*Seventeen Patients with Ureteral Ectopia Seen from 1933 Through 1956 at the Squier Urological Clinic, Columbia-Presbyterian Medical Center*

Case No.	Year	Age	Sex	Diagnosis	Treatment	Current Status
1	1933	8 mo.	F	Bilateral ureteral ectopia in urethra; bilateral duplication upper urinary tract	Left heminephrectomy and partial ureterectomy	Unknown
2	1939	7 yr.	F	Right ureteral ectopia in urethra; double right upper urinary tract	(1) heminephrectomy and partial ureterectomy; (2) removal of ureteral stump 11 months after first operation	Unknown
3	1942	3 wk.	F	Right ureteral ectopia in urethra; double right upper urinary tract	(1) right ureteroneocystostomy, (2) right heminephrectomy and ureterectomy 6 yr. after first operation	Unknown
4	1944	1 yr.	F	Right ureteral ectopia in vagina; double right upper urinary tract	Right nephrectomy and partial ureterectomy	Good
5	1945	2 mo.	F	(1) Rectovaginal fistula, (2) incomplete duplication of sigmoid colon, (3) left ureteral ectopia in sigmoid; upper urinary tracts normal	(1) left nephrectomy and partial ureterectomy, (2) removal of ureteral stump, (3) partial colectomy; 1 mo. and 2 yr. respectively after first operation	Good
6	1947	3½ yr.	F	Right ureteral ectopia in urethra; double right upper urinary tract	(1) Right heminephrectomy and partial ureterectomy, (2) Excision of ureteral stump 8 months after first operation	Good
7	1947	5 yr.	F	Left ureteral ectopia in urethra; double left upper urinary tract	Left ureteroneocystostomy	Feels well but upper half of left kidney is not visualized by IVP
8	1951	41 yr.	M	Right ureteral ectopia in posterior urethra; double right upper urinary tract	Renal exploration and biopsy; double right kidney with inoperable papillary carcinoma	Died in 1951 of carcinoma of upper right renal pelvis with diffuse metastases
9	1951	23 yr.	F	Right ureteral ectopia in vagina; double right upper urinary tract	Right heminephrectomy and partial ureterectomy	Good
10	1951	9½ yr.	F	Ectopic left ureteral opening in vagina; double left upper urinary tract	Left heminephrectomy and complete ureterectomy	Cured
11	1953	12 yr.	F	Right ureteral ectopia in urethra; double right upper urinary tract	Right upper heminephrectomy and partial ureterectomy	Good
12	1953	3 yr.	F	Left ureteral ectopia in urethra; bilateral duplication of upper urinary tract	Supportive	Died in 1953 of biliary atresia
13	1954	9 yr.	F	Right ureteral ectopia in vagina; upper urinary tract normal	Right nephrectomy and partial ureterectomy	Good
14	1955	3½ yr.	F	Left ureteral ectopia in urethra; double left upper urinary tract	Left heminephrectomy and partial ureterectomy	Good
15	1955	8½ yr.	F	Right ureteral ectopia in vagina; bilateral duplication of upper urinary tract	Left heminephrectomy and partial ureterectomy	Good
16	1955	7 wk.	F	Left ureteral ectopia in vagina; double left upper urinary tract	Left heminephrectomy and partial ureterectomy	Good
17	1956	22 yr.	M	Aplastic single pyelonephritic right kidney with its ureter emptying in right seminal vesicle; double left kidney and ureter with the supernumerary ureter emptying in left seminal vesicle	Supportive	Died in 1956 of renal failure and hypertension

substantiated on pathological examination of the surgical specimens.

Radiographic and Cystoscopic Findings.—The following radiographic studies were performed: a plain film of the abdomen in every case, intravenous urography in 16, and retrograde pyelography of the anomalous tract in seven (Fig. 1, *A* and *B*). Urethral and vaginal examinations were performed in 15 patients in order to determine the presence of the ectopic ureteral opening. The ectopic orifice was visualized in seven patients but was not discovered in five. In the remaining three patients an

TABLE 2.—*Sex and Age in Seventeen Cases of Ureteral Ectopia*

Sex	Male *	Female
Cases	2	15
Ages	22-41 yr.	3 wk.-23 yr.

* Both male patients died and the ureteral ectopia was discovered at autopsy.

TABLE 3.—*Symptoms and Signs in Seventeen Patients with Ectopic Ureteral Orifice*

Symptoms and Findings	Patients
Pyuria	9
Incontinence	8
Fever	7
Dysuria	2
Fecaluria	1
Enuresis	1
Vaginal discharge	1
Gangrene of toes	1
Hematuria	1

attempt to visualize by injection what was thought to be the ectopic orifice was unsuccessful. A urethrogram, however, disclosed in Case 4 the ectopic ureter which previously had not been located by urethroscopy. In Case 17, because of the high levels of blood urea nitrogen and the misleading clinical picture with which the patient was admitted to the hospital, neither intravenous urography nor retrograde pyelography was performed, nor was the presence of an ectopic ureteral opening suspected. In Case 8, a plain film of the

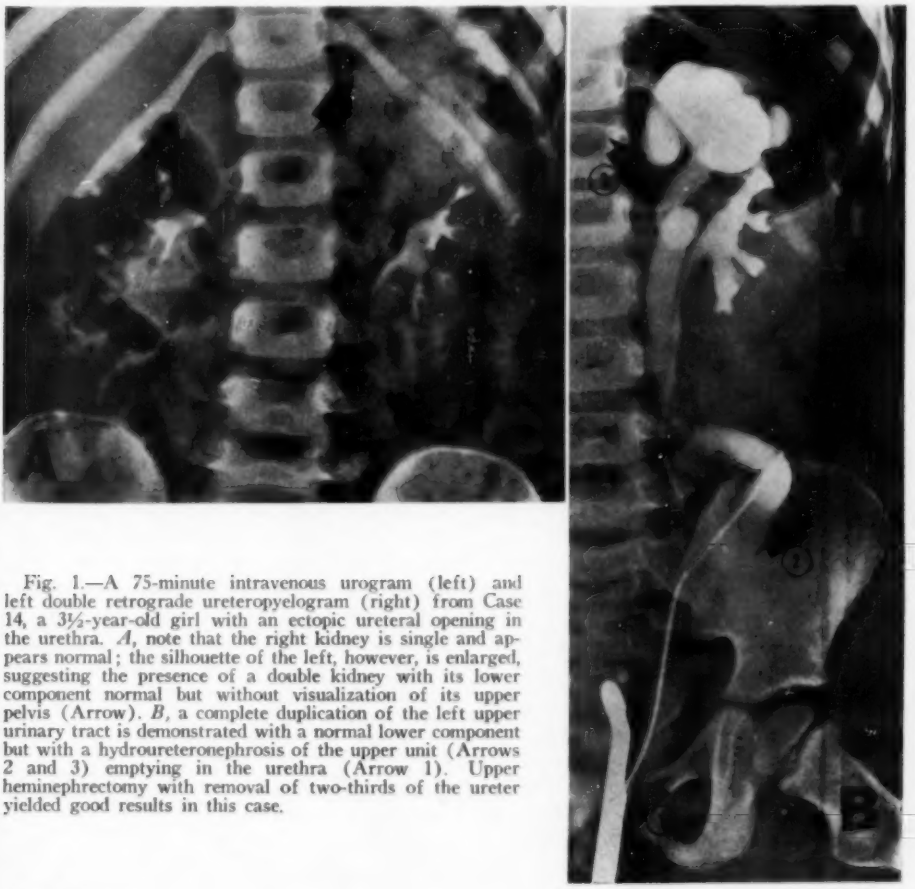

Fig. 1.—A 75-minute intravenous urogram (left) and left double retrograde ureteropyelogram (right) from Case 14, a 3½-year-old girl with an ectopic ureteral opening in the urethra. *A*, note that the right kidney is single and appears normal; the silhouette of the left, however, is enlarged, suggesting the presence of a double kidney with its lower component normal but without visualization of its upper pelvis (Arrow). *B*, a complete duplication of the left upper urinary tract is demonstrated with a normal lower component but with a hydroureteronephrosis of the upper unit (Arrows 2 and 3) emptying in the urethra (Arrow 1). Upper heminephrectomy with removal of two-thirds of the ureter yielded good results in this case.

TABLE 4.—*Anatomical Classification of the Types of Ectopic Ureteral Orifice According to Number of Renoureteral Units and Position of the Ectopic Ureteral Orifice(s).*

Types	Cases	Urethra	Vagina	Rectum	S. V.*
Unilateral duplication with one ectopic ureteral orifice	11	6	5	0	0
Single ureter with ectopia	1	0	0	1	0
Unilateral duplication with ureteral ectopia of the supernumerary ureter and ectopia of the contralateral single ureter	1	0	0	0	1
Bilateral duplication with one ectopic ureteral orifice	2	1	1	0	0
Bilateral duplication with bilateral ectopia of the supernumerary ureters	1	1	0	0	0
Unilateral duplication with ectopia of both ureteral openings	1	1	0	0	0
Total	17	9	6	1	1

* Seminal vesicles.

abdomen disclosed a calcified ring-like structure at the level of the upper pole of the right kidney. Upon surgical exploration, a double right kidney with a partly calcified neoplasm arising from the upper renal pelvis and invading the retroperitoneum was found. At cystoscopy, blood had been seen in the posterior urethra and clear urine in the bladder, but the ectopic ureteral opening could not be visualized at that time.

Site of the Ectopic Ureteral Opening and Status of the Upper Urinary Tract.—According to Table 4, the urethra was the site of ureteral ectopia in nine patients, the vagina in six, the rectum in one, and the seminal vesicles in another. Ureteral ectopia was frequently found associated with ipsilateral or bilateral duplication of the upper urinary tract, and the ectopic ureteral opening was always the one which drained the upper half of the involved kidney. In Case 5 an ectopic ureteral opening in the rectum without duplication of the involved upper urinary tract but with partial duplication of the sigmoid colon, and a rectovaginal fistula were present. This unusual case presented a difficult problem in diagnosis and therapy.

Treatment and Results.—As shown in Table 5, heminephrectomy with partial or total ureterectomy was carried out in 10 patients and nephrectomy with partial ureterectomy in three. Secondary excision of the remaining ureteral stump had to be done in three cases because of persistent pyuria, fever, or dysuria. In two patients, Cases 3 and 7, ureteroneocystostomy of the ectopic ureter was performed. However, in Case 3 secondary nephroureterectomy had to be carried out six years later because of persistent urinary infection and hydronephrosis. In Case 7, a recent intravenous urogram failed to visualize the renal unit from which the anomalous ureter was transplanted into the bladder in 1947. Nevertheless, this girl feels well at present, and further intervention has been deferred. In one patient (Case 8) renal exploration with biopsy of an inoperable carcinoma arising from the anomalous renal pelvis was done. Two patients, (Cases 12 and 17) had supportive treatment only. In the last three patients the ectopic ureteral opening was clinically unsuspected but discovered at necropsy. The current status of three patients (Cases 1, 2, and 3) is unknown. Good results have been verified in Cases 4, 5, 6, 9, 10, 11, 13, 14, 15, and 16.

Pathological Findings.—The pathological findings of the involved kidney are shown

TABLE 5.—*Operations Carried Out in Fifteen of the Seventeen Patients with Ectopic Ureteral Opening* *

Surgical Procedure	No. of Procedures
Heminephrectomy (10)	
(a) partial ureterectomy	9
(b) total ureterectomy	1
Nephrectomy with partial ureterectomy	3
Secondary excision of ureteral stump	3
Ureteroneocystostomy	2
Renal exploration and biopsy of kidney tumor	1
Total	19

* Two patients had no surgical treatment.

TABLE 6.—*Anomalies and Pathological Lesions of the Involved Kidney in Seventeen Patients with Ectopic Ureteral Opening*

	No. of Specimens
Double kidney	12
Pyelonephritis	12
Hydronephrosis	11
Renal hypoplasia	8
Ureteritis	2
Renal cysts	1
Papillary carcinoma of the renal pelvis	1

in Table 6. They consisted of pyelonephritis, renal hypoplasia, hydronephrotic atrophy, and double kidney.

Brief Historic Review

In 1843, Civiale [1] was the first to report a case of complete unilateral duplication of the upper urinary tract with an ectopic opening of the supernumerary ureter into the posterior urethra. Since then numerous reports on the subject have appeared in the medical literature with increasing frequency. In 1936 Crenshaw [2] stated that the incidence of this anomaly at the Mayo Clinic was 1 in 85,150 births. In 1949 Burford et al.[3] reviewed the medical literature on the topic and found 425 reported cases of ectopic ureteral opening. According to them, females outnumbered males in a ratio of 5 to 1, and 88.8% of the patients were less than 30 years of age. Also, both ureters, as already stated by Abeshouse,[4] were equally involved. In Burford's report the ectopic ureteral orifice in males was found most commonly in the posterior urethra; then, in descending order of frequency, in the seminal vesicles, prostatic utricle, ejaculatory ducts, and vas deferens. In females the location was listed in the following order of frequency: the vaginal vestibule, urethra, vagina, cervix, and uterine cavity. Burford reported that 61.3% of the cases with ureteral ectopic orifice also had duplication of the upper urinary tract, and that the ectopic ureter was always the one draining the upper renal pelvis.

In 1954, Katzen and Trachtman [5] stressed the value of filling the vagina with a contrast

TABLE 7.—*Results* *

	No. of Cases
Good results	10
Fair results	1
Unknown	3

* In the remaining three cases the ureteral ectopia was discovered at necropsy.

medium (vaginogram) for the purpose of outlining the ectopic ureter by regurgitation. This procedure may be helpful, particularly in those cases with relatively normal upper urinary tracts and nonvisualization of the ectopic orifice. The urethra may also be distended with contrast medium by retrograde filling, or preferably by voiding cystourethrograms as pointed out by Kjellberg et al.,[6] which then, by refluxing up into the ureter, will outline it on the radiograph. In one of our patients (Case 2) the ectopic ureter was visualized by retrograde filling of the urethra with 40% iodopyracet (Diodrast). In two other instances, although the same procedure was used, the results were unsuccessful.

When the suspected ectopic ureter opens into the seminal vesicle, then a seminal vesiculogram obtained via the ejaculatory ducts or through the vasa deferentia, as recommended by Goldstein and Heller,[7] may yield the desired information. These authors in 1956 reported the "10th" case of ectopic ureteral opening into a seminal vesicle, diagnosed clinically by seminal vesiculography. Young [8] in 1955 stated that the presence of a soft mass on top of the seminal vesicle and a cystic swelling in the bladder base along with absence of a ureteric orifice, hemitrigone, and nonvisualization of the ipsilateral kidney by intravenous urography, are suggestive findings of an ectopic ureteral opening into a seminal vesicle. Extension of the opaque medium upward and along the ureter on vesiculography will, if present, confirm the suspicion.

Williams [9] in 1951, Brockis [10] and Moore [11] in 1952, separately gave interesting embryological accounts of the various structures and mechanisms which partake in the

genesis of this anomaly. In 1954 Williams [12] also made a comprehensive study of the diverse urographic patterns observed in 11 cases with ectopic ureteral openings.

Cases of ectopic ureteral orifice and megaloureter [13]; ectopic ureter not causing incontinence until adulthood [14]; ectopic ureteral opening into a dilated Gartner's duct [15] and into a cystic diverticulum of the ejaculatory duct,[16] and solitary kidney with ectopic ureteral orifice in a child with agenesis of the abdominal musculature [17] have been reported.

Embryological Account

Ureteral ectopia, ureterocele, stenosis of the ureteral ostium, some types of congenital bladder neck obstruction and complete or incomplete duplications of the upper urinary tract are the end-results of deviations from the normal embryogenesis of the mesonephric duct and its derivatives. Detailed description of the development of the mesonephric ducts and related structures can be found in standard textbooks [18,19] or other publications dealing with this problem.[9-11] Therefore, we shall make no attempt to present an exhaustive review of this subject, but rather to sketch, as we understand it, the embryological development of the ureter, from the beginning until its incorporation into the bladder wall.

In embryos of about 5 mm. in length (4 weeks), the ureter appears as a bud on the dorsal side of the mesonephric or Wolffian duct, near its entrance to the cloaca (Fig. 2, *A*). The ureteral bud grows dorsally and cephalad until it joins the metanephric blastema (permanent kidney). The renal pelvis, calyces and collecting uriniferous tubules result from subsequent expansions and fan-like divisions of the ureteral bud in its ascending progression toward its final achievement, namely, union with the distal end of the distal convoluted tubules in the metanephros. The development patterns of the lower ends of both the mesonephric duct and the ureter are less clearly understood.

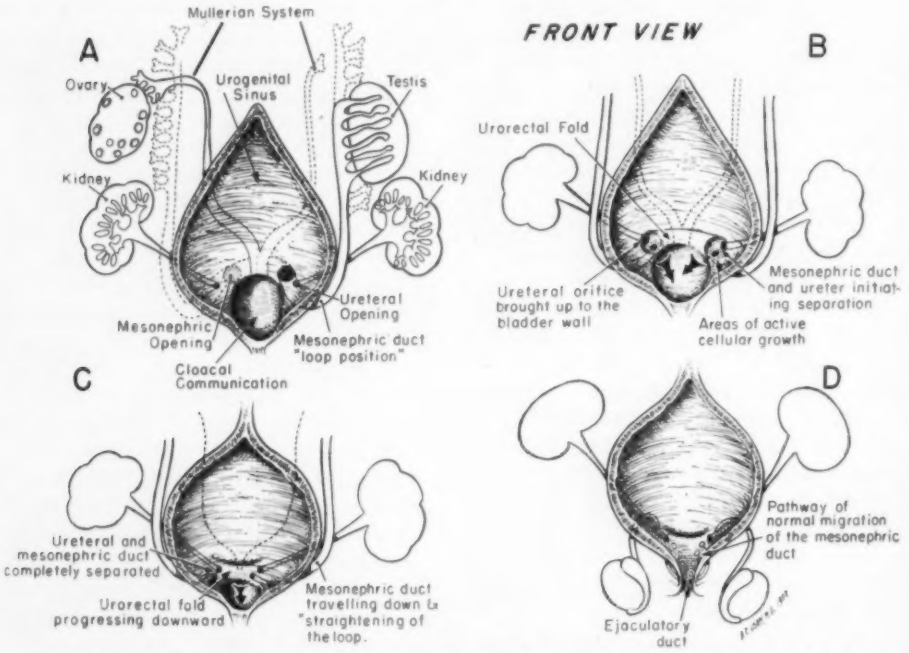

Fig. 2.—Schematic representation of the embryogenesis of the lower end of the mesonephric duct. (For explanation see text on "Embryological Account.")

At about the 11 mm. (6 weeks) stage of the human embryo's development, a great expansion of the urogenital sinus (the forerunner of the bladder) takes place. At the same time, the ureteral openings which were situated on the dorsal aspect of the mesonephric ducts come down into direct contact with the wall of the urogenital sinus and into its inner surface (Fig. 2, *B*). In the 15 mm. (7 weeks) embryo the openings of the mesonephric ducts and the ureters are found close to one another in the posterior wall of the urogenital sinus where it can be seen that the ureteral orifices lie beside the mesonephric openings (Fig. 2 *B, C*). The mechanisms whereby the mesonephric ducts migrate toward the lower end of the urogenital sinus (posterior urethra) and the process of separation of the ureters from the mesonephric ducts and their simultaneous incorporation into the bladder wall are not fully understood. However, several hypotheses have been advanced. One is that of the "mesonephric migration" along with the progressive downward growth of the urorectal fold. Thus, once the cloaca or communication between the urogenital sinus and rectal ampulla has been occluded (Fig. 2 *C, D*), then the lower ends of both mesonephric ducts are transposed to the posterior urethra and converted thereby into the ejaculatory ducts. Simultaneously the trigone emerges as a result of steady accumulation of mesodermal structures derived from the urorectal fold and mesoderm surrounding the mesonephric ducts. The trigone, therefore, will occupy a position between the ureteral openings and the ejaculatory ducts. Another hypothesis is the theory of "an active growth area" which centers around the upper and outer lip of the orifice of the mesonephric duct. In this area the epithelial cell layer is thicker and, according to Brockis,[10] appears to be dividing actively. Separation of the ureter from the mesonephric ducts is said to be due mainly to this mechanism. The concept of the "straightening loop" as advocated by Williams[9] is also an interesting one. According to this author, the orifice of the mesonephric ducts is transposed progressively from the bladder wall, down to the vertex of the urogenital sinus by a gradual straightening of the "mesonephric loop" as a result of an active growth of the mesodermal structures and the growth of the urogenital sinus as a whole. According to this theory the shape of the lower end of the mesonephric duct merely changes from one of a "cane" to that of a straight stick (Fig. 1 *A, C*). This end of the mesonephric ducts apparently does not grow in length because with its original "loop" configuration it is long enough to reach the posterior urethra. Perhaps all three described mechanisms partake in the embryological development of these structures.

The ureter remains attached to the mesonephric duct until about the 15 mm. stage. The full separation of both organs with subsequent incorporation of the ureter into the bladder wall and transposal of the mes-

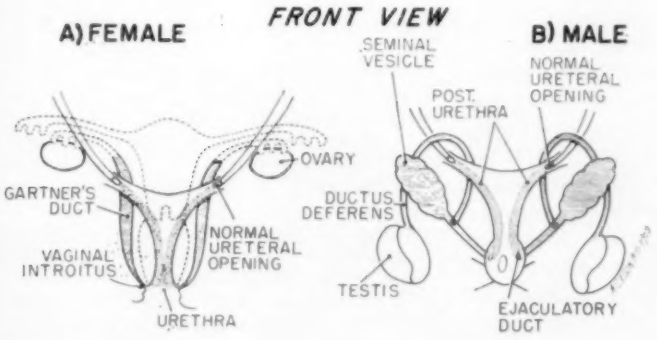

Fig. 3.—Dotted and shaded areas indicate where an ectopic ureteral opening may occur. *A*, in female; *B*, in male.

onephric duct (future ejaculatory ducts) into the posterior urethra in the male or into the vestigial organs in the female is not completed until about the fourth month of fetal development. If this separation fails, then an ectopic ureteral opening emerges, and it may be found anywhere from the trigonal corners to the ejaculatory ducts (posterior urethra) or in the seminal vesicles and ductus deferens in the male and in the urethra, vagina or in any of the Wolffiian vestigals (Gartner ducts, etc.) in the female (Fig. 3, *A* and *B*, shadowed areas).

Summary

A report based on a review of the clinical records of 17 cases of ectopic ureteral opening is presented. The various clinical pictures, anatomical types of ectopia, methods of treatment, pathological lesions in the involved kidney, and the results obtained after treatment have been tabulated and discussed in detail. The available literature on the subject and the essentials on embryological development of the lower end of both the mesonephric duct and the ureter have also been reviewed.

Recognition of ectopic ureteral opening may be difficult. Its clinical manifestations are at times paradoxical and misleading. The classical symptom complex of incontinence with intermittent normal voidings was present in only 8 of the 15 female patients in our series, and in none of the males. Bouts of fever and pyuria, not otherwise explained, were found to be suggestive. In males the symptoms are often bizarre. Complete evaluation of a child suspected of having this anomaly should include the radiographic demonstration of the ectopic ureter. Repeated intravenous pyelograms with delayed exposures may help in outlining the anomalous tract.

Ureteroneocystostomy is indicated in cases of bilateral ureteral ectopia without duplication of the upper urinary tract. In patients with duplication of the upper urinary tract the anomalous ureter may be transplanted into the bladder (ureteroneocystostomy) or into the normal ureter or pelvis (ureteroureterostomy or ureteropyelostomy). The treatment of choice, however, is heminephrectomy or nephrectomy with complete ureterectomy, particularly if the ureter appears to be dilated and infected. In other instances heminephrectomy or nephrectomy with partial ureterectomy may suffice. Because of the danger of progressive hydroureteronephrosis, infection, and even rupture of the anomalous ureter, ligation of this organ is not recommended for the treatment of this anomaly.

620 W. 168th St. (32).

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Observations on a Baby Born to a Mother with Congenital Adrenal Hyperplasia

ZVI LARON, M.D., Petah Tikva, Israel

Since the introduction of cortisone as treatment of the adrenogenital syndrome by Wilkins et al.[1] only three women with congenital adrenal hyperplasia, including one from this hospital, have been reported to have given birth to a live baby.[2-4]

Considering the problems presented by the baby of a mother with the adrenogenital syndrome, a disease generally considered inheritable,[5] and in particular the possible damage to the fetus by prolonged administration of cortisone to the pregnant mother, it seems justified to present the metabolic and endocrine studies performed on such a baby born in our hospital.

Report of Case

The patient's mother came under medical attention at the age of 16 years, because of hirsutism and amenorrhea, and was found to have a very enlarged clitoris and a urogenital sinus. She had had pubic and axillary hair since the age of 3 years. She was considered to have female pseudohermaphroditism due to congenital adrenogenital syndrome. Cortisone therapy was instituted and clitoridectomy and vaginoplasty performed. Her explicit case history has been published by Ser and Gans.[4,6]

Three and a half years after continuous cortisone therapy, 100 mg. intramuscularly every fourth day, she became pregnant. Cortisone therapy was continued as before. Five days before delivery urinary 17-ketosteroids were 19.5 mg. per 24 hours. At term a live baby was delivered by cesarean section, performed after administration of an extra 200 mg. of cortisone. After delivery the level of 17-hydroxycorticosteroids in the mother's plasma was 26μg. per 100 ml.

The baby was seen by us at delivery. She was a baby girl who cried immediately. There was no cyanosis. Her weight was 3,350 gm., length 50 cm. and head circumference 35 cm. She had slight mammary hyperplasia, and the liver was palpable 2 cm. below the costal margin. The heart rate was 148 per minute. There was no hyperpigmentation and no cleft palate. The genitalia were of normal appearance.

In consideration of the possibility of adrenal insufficiency in the baby because of prolonged cortisone therapy to the mother, the baby was started on cortisone 5 mg. t. i. d. by mouth and corticotropin (ACTH) 2 units t. i. d. intramuscularly. From the second day of life she was breast fed until the ninth day, when she was put on half-strength cow's milk because of insufficient lactation.

Figure 1 shows some of the data collected during the baby's first two weeks of life. After the physiologic loss of weight, birth weight was again reached at two weeks. The number of total eosinophils was elevated after birth and fell after the administration of steroids. There was some temporary elevation again after cortisone was stopped. The serum sodium concentration fell, and serum potassium concentration rose slightly after cessation of corticotropin administration. Urine collected on a metabolic bed showed an increase in volume during the administration of steroids. The electrolyte balance was calculated by substracting the electrolytes excreted in the urine from the calculated intake. As the electrolyte excretion by

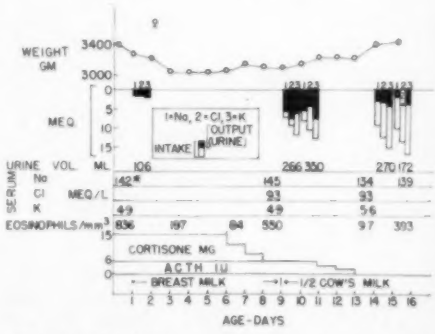

Fig. 1.—Metabolic data during the first two weeks of life. Asterisk indicates cord blood.

Submitted for publication Dec. 4, 1958.

Department of Pediatrics and the Medical Research Institue of the Labour Sick Fund, Beilinson Hospital, Petah Tikva, Israel.

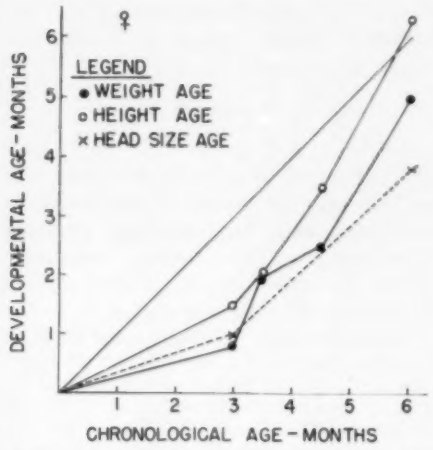

Fig. 2.—Physical development of patient during the first six months of life related to the 50th percentile of normal standard.

the gastrointestinal tract is minimal under normal conditions, feces were not analyzed. The intake being unknown while the infant was on breast milk, only the output has been charted on the second day of life. It is evident that in spite of an increased intake, the urinary excretion of sodium and chloride and also of potassium decreased after corticotropin was discontinued.

The plasma concentrations of 17-hydroxycorticosteroids (17-OHCS) measured on several occasions are shown in Table 1. The high level in the mother's plasma is evidence of the adequate dose of cortisone administered. The concentration of 17-OHCS in the cord blood was much lower than that of the mother's blood at the same time, the ratio being 3:1. At the age of 11 days, in spite of continued corticotropin administration intramuscularly and 2 units given intravenously two hours prior to drawing the blood, the plasma level of 17-OHCS was very low. At the age of 2½ months the intravenous corticotropin test was repeated, and this time a marked rise of the 17-OHCS was observed. Table 2 shows the measurements of urinary steroids performed on days 10 and 16; i. e., during corticotropin administration

TABLE 1.—*Plasma 17-Hydroxycorticosteroids*

	μg. %
Mother 6 minutes after delivery	20
Baby at birth — cord blood	8
Age 11 days corticotropin I. M. 2 hours after 2 U. I. V.	2
Age 10 weeks before corticotropin	1.4
2 hours after corticotropin 2 U. I. V.	44.5

and three days after its discontinuation. It is evident that the 17-KS excretion was normal and the 17-OHCS excretion very low. Pregnanetriol and pregnanetriolone excretion were not increased.

At birth the blood hemoglobin was 17.3 gm. %, the red blood cells 5,100,000 per cubic millimeter and the white blood cells 22,100 per cubic millimeter. At 2 weeks of age the hemoglobin was 13 gm. %; the red blood cells 3,700,000 per cubic millimeter, and the white blood cells 15,600 per cubic millimeter.

The baby was discharged in good physical condition on Day 17. At the age of 2 months she had a lower urinary tract infection followed by infectious diarrhea. She was admitted to the hospital and was successfully treated with antibiotics. Her physical development until age 6 months can be seen first from Figure 2. At 6 months her weight was 6,800 gm., length 66 cm., and head circumference 40 cm. She was rolling over and trying to sit up. She was interested in her surroundings and grasped toys. The anterior fontanelle was open 1.5 cm., and she had no teeth as yet.

TABLE 2.—*Urinary Steroids in Baby*

Age (days)	10	16	
Therapy	Corticotropin	0	
17-KS	1.1	0.7	mg./24 hr.
17-OHCS	0.16		mg./24 hr.
Neutral Fluorogenic Subst.	0.56		mg./24 hr.
Pregnanetriol	190	80	μg./24 hr.
Pregnanetriolone	0	8	μg./24 hr.

The liver was still palpable at about 1.5 cm. The genitalia were normal. Laboratory examinations at this time showed the following: blood urea concentration 30 mg/100 ml.; serum sodium 139 mEq/L.; Cl 101 mEq/L.; K 4.1 mEq/L.; serum total protein concentration 7.8 gm/100 ml., albumin 4.8 gm/100 ml., globulin 3.0 gm/100 ml. The electrophoretic pattern of the serum proteins was as follows: albumin 56.3%; α_1-globulin 5.7%; α_2-globulin 9.4%; β-globulin 13.1%; γ-globulin 12.6%. The serum calcium was 10.6 mg/100 ml.; inorganic phosphorus 5.8 mg/100 ml.; alkaline phosphatase 12.2 B. U/100 ml.; P. B. I. 4.4μg/100 ml. Roentgen examination of the left wrist revealed two carpal ossification centers.

Comments

The familial occurrence of congenital adrenal hyperplasia led Childs et al.[7] to suggest that the disorder may be due to recessive traits which express themselves only in the homozygous offspring. Their assumption of recessive inheritance is

strengthened by the present observation that the offspring of a woman with the adrenogenital syndrome was a baby of normal appearance, excreting normal quantities of pregnanetriol and pregnanetriolone even after corticotropin stimulation. Dominant inheritance of this disorder is suggested, however, from cases described in first cousins.[8]

The finding of a normal baby is also of interest in view of the fact that the mother had received 100 mg. of cortisone every fourth day throughout pregnancy. There are reports on cleft palate in fetuses following the administration of cortisone to pregnant mice,[9,10] and in two instances in humans when pregnant mothers suffering from steatorrhea [11] or lupus erythematosus [12] had received cortisone up to 300 mg. daily. On the other hand, an Addisonian woman, receiving 12.5 to 25 mg. cortisone per day, delivered a normal baby.[13] It is apparent that cortisone, given as replacement therapy in a physiological dose range, does not cause congenital malformations.

We have found only one report of an infant displaying clinical evidence of hypoadrenalism, whose mother had received cortisone until delivery.[14] The administration of cortisone and corticotropin to the baby described here may have prevented the appearance of signs of adrenal insufficiency, but we cannot be certain whether these steroids were required. Nevertheless, there is little doubt that the negative response of the plasma 17-OHCS to corticotropin stimulation on the 11th day of life points to a prolonged adrenal nonresponsiveness, as Klein [15] has found a good response in normal infants as early as the age of 3 days. At 2½ months the presently described baby had a normal adrenal response to corticotropin. Increased urine and electrolyte excretion during the first days of life upon administration of corticotropin was shown by Klein to occur even in normal newborns.[16]

Certainly more and more babies will be born to parents with the congenital adrenogenital syndrome. Clinical observations and laboratory studies on these babies will help clarify the problems discussed.

Summary

Metabolic and endocrine studies have been performed on a female baby born to a mother with the congenital adrenogential syndrome who had received cortisone throughout pregnancy. Besides a temporary adrenal nonresponsiveness to corticotropin stimulation, the baby was normal.

I am indebted to Dr. A. F. Muller and Dr. M. C. Sanz from the Hôpital Cantonal, Geneva, Switzerland, who performed the microdetermination of the plasma 17-hydroxycorticosteroids and to Dr. M. Finkelstein of the Hadassah-Hebrew University Medical School, who measured the urinary pregnanetriol and pregnanetriolone. Thanks are also due to Dr. Z. Yonis for his interest in the present study and to Dr. A. de Vries for his help in the preparation of the manuscript.

Beilinson Hospital.

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Infectious Hepatitis

Correlation of Clinical and Laboratory Findings, Including Serum Enzyme Changes

OSCAR BODANSKY, M.D.; SAUL KRUGMAN, M.D.; ROBERT WARD, M.D.; MORTON K. SCHWARTZ, Ph.D.; JOAN P. GILES, M.D., and A. MILTON JACOBS, M.D., New York

The high incidence of infectious hepatitis during World War II and the immediate postwar years led to many clinical and laboratory studies of this disease.[1-4] Since it was not transmissible to laboratory animals, several investigations in which the infectious agent was administered to human volunteers made it possible to define more clearly the clinical course of the disease and its correlation with changes in various laboratory parameters.[5-10] At about this time it was also shown that γ-globulin conferred passive immunity against infectious hepatitis.[11,12]

More recently it has been reported that in institutional outbreaks of hepatitis, persons who received γ-globulin were apparently protected for periods as long as seven to eight months.[13-15] Stokes and his associates[15] postulated that during the early period of passive protection from γ-globulin, the patients were exposed to hepatitis virus and that subclinical infection was followed by the development of active immunity. In 1956 several of us initiated studies to control the high incidence of infectious hepatitis in an institution for mentally defective children.[16,17] In order to test Stokes' hypothesis, one aspect of these studies was concerned with an attempt to induce "passive-active" immunity by the administration of γ-globulin and hepatitis virus under carefully controlled circumstances and close observation.

The present investigation was directed chiefly toward the correlation of clinical manifestations of the artificially induced disease with changes in conventional biochemical tests of hepatic function and in certain serum enzyme activities. The use of the latter as criteria of hepatic damage has been developed within the past few years[18-20] and was not available in the clinical-laboratory correlative studies in induced infectious hepatitis in the 1940's. Of particular relevance to our study was the establishing of a set of criteria which would permit the definitive diagnosis, not only of cases of hepatitis with varying clinical manifestations but also of subclinical cases. Such subclinical cases might occur, as postulated by Stokes, during the early part of the period following the conjoint administration of virus and γ-globulin.

In pursuance of these aims we have determined the relationships between the magnitude of the administered dose of a hepatitis virus preparation and (*a*) the frequency of abnormal clinical and laboratory findings; (*b*) the extent of change in quantitatively measurable parameters, such as the concentration of bilirubin in the serum, the thymol turbidity, and the activities of

Submitted for publication Dec. 16, 1958.

Present address of Dr. Ward: Department of Pediatrics, University of Southern California, Los Angeles.

From the Division of Metabolism and Enzyme Studies, Sloan-Kettering Institute for Cancer Research; the Department of Pediatrics, New York University College of Medicine, and the Willowbrook State School, Staten Island, New York. This study was conducted under the sponsorship of the Commission on Viral Infections, Armed Forces Epidemiological Board. The investigation was supported in part by the Office of the Surgeon General, Department of the Army; Research Grants T-18 and P-164A from the American Cancer Society; Research Grants 332B and 332C from the Damon Runyon Memorial Fund.

the various serum enzymes. Comparisons have been made among these various parameters with respect to (*a*) the time of their elevation after administration of virus; (*b*) the extent of such elevations, and (*c*) the time of emergence and recession of the clinical manifestations. The set of diagnostic criteria that resulted from the preceding studies has been applied to an evaluation of the frequency and time of occurrence of hepatitis in children receiving various doses of virus, in children not receiving virus but in contact with those that had received it, and finally in children to whom virus and γ-globulin were administered conjointly.

Methods and Materials

Clinical Material.—The nature of the endemic hepatitis occurring at the Willowbrook State School and involving both inmates and attendants has previously been described in detail.[37] Although the annual attack rate has been high, about 20 to 25 per 1,000, the disease is mild and no deaths attributable to it have occurred since 1953.

The patients in the study group, 5 to 10 years of age, were newly admitted to the Willowbrook Institution and brought directly to an isolation unit capable of housing up to 16 children. They had no contact with the rest of the institution and were cared for by physicians, nurses, and attendants who had minimal contact with other patients and personnel. The several factors that were weighed in making the decision to feed virus to some of these patients, the preparation of the virus, the tests used to determine its safety, and the close controls attending all trials, have been previously described in detail.[37] The plan was sanctioned by the authorities of the New York State Department of Mental Hygiene and by the Armed Forces Epidemiological Board. Parental permission was obtained in every instance.

The present study includes 99 children. The effects of doses ranging from 1 gm. to 4 gm. of a heated virus preparation, WBRK No. 1, was determined in 45 cases; 11, serving as controls, received no virus. Various subgroups of these 56 children served as controls for other phases of the study. In addition, 10 subjects were given 0.1 gm. of the unheated virus preparation, WBRK No. 1. Thirteen received 0.1 gm. of an unheated preparation obtained from the stools of three patients approximately 15 days before clinical hepatitis developed and twenty children received a conjoint administration of 2 gm. of the heated virus suspension and 0.06 ml. γ-globulin per pound of body weight.

Clinical Criteria.—The incubation period of various outbreaks of infectious hepatitis has been estimated to range usually from 20 to 40 days. We have previously noted that in a group of children, placed in an isolation unit and given hepatitis virus, some exhibit abnormal clinical and laboratory findings at about 30 to 50 days after such administration, whereas other members of the group show these findings 60 to 70 days after administration.[37] Subsequent studies by us have indicated that those children showing manifestations of the disease at 60 to 70 days had been infected secondarily from those having signs of the disease at about 30 to 50 days.

The symptomatology of infectious hepatitis has been described in detail.[3-6] Obviously, subjective symptoms could not be obtained from the population of mentally defective children. The following three diagnostic criteria for overt hepatitis were used in the present work and were defined as follows: ***fever,*** a temperature of 101 F or higher for at least 24 hours occurring between 30 and 50 days after the administration of the virus and due to no other discernible cause; ***hepatomegaly,*** an *increase* of 2 cm. or more in the size of the liver below the costal margin between 30 and 50 days after administration of the virus; ***jaundice,*** appearance within the stated period of a definite yellow hue in the sclerae of Negro children, and in the sclerae and skin of white children. Observations concerning the appearance of jaundice were made without knowledge of the laboratory findings and did not include impressions of "slight tint" or "muddy color."

Conventional Biochemical Tests of Liver Function.—Blood was drawn before the administration of virus and routinely at weekly intervals during the incubation period. While the disease was becoming manifest or running its course, samples at two- to three-day or even daily intervals were obtained.

Although it would have been desirable to perform in many instances a variety of biochemical tests for hepatic function, such as total and free cholesterol, sulfobromophthalein (Bromsulfalein) retention, and alkaline phosphatase, in addition to those finally decided upon, the amounts of blood required and the frequency of bleedings would not have been consistent with the welfare of the child. Two conventional biochemical tests were performed: that of Malloy and Evelyn[38] for serum bilirubin, and that of MacLagan[39] for thymol turbidity. Because of the limited personnel and complexities in the processing and transportation of the blood from the State School, it was not possible to perform cephalin flocculation tests in all instances within a reasonable time after blood collection. The appearance of spurious positive tests in sera more than one day old is well ap-

preciated.[28] Consequently, no results for cephalin flocculation are included in the present report.

Although the normal ranges for these determinations have been established in several studies in adults, it was considered advisable to determine the range of normal values in the population of children used in the present study and in related studies that will be reported later. The values in 95 children *prior to administration of virus* were averaged and yielded the following results:

	Normal Mean Value	Standard Deviation (S. D.)	Upper Limit of Normal
Bilirubin	0.50 mg/100 ml.	0.21 mg/100 ml.	1.0 mg/100 ml.
Thymol turbidity	2.3 units	0.86 units	4.5 units

As may be seen, the upper limit of normal was taken as 2.5 S. D. above the mean value; only 1% of normal values would, therefore, fall above these limits.

Serum Enzyme Determinations.—The relationships between the development of hepatitis and the activities of five different serum enzymes: phosphohexose isomerase (PHI), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), lactic acid dehydrogenase (LAD), and alkaline phosphatase (P'ase), were considered in the present study. Because of the limited amounts of blood available, not all of these enzymes were studied at the same time. In some groups one enzyme was studied, and in others two or three enzyme activities were determined concurrently so as to permit comparison of their changes. The upper limit of normal for each enzyme was taken as two and a half standard deviations above the normal mean value. All enzyme determinations were performed at 37 C.

PHI mediates the reversible conversion of glucose-6-phosphate to fructose-6-phosphate. The method for its determination in serum has been previously described in detail.[24] The serum enzyme is stable at both normal and high activities for at least six months in the freezer. The normal mean value for adults is 21 units, with a standard deviation of 7.0 units. The mean value for 68 children in this study was found to be 40 units, with a standard deviation of 16 units. The criterion of abnormality for this enzyme activity was therefore taken as a rise from the normal range to a level 2.5 S. D. above the mean, i. e., 80 units.

GOT activity was determined by the method of Karmen,[25] with some slight modifications. When kept in the freezer at —10 C to —20 C, this serum enzyme is stable at normal activities for at least 10 months, and at high activities for approximately 4 months. Because of the small amounts of blood available, 0.1 ml. serum was used in a final reactant volume of 3.0 ml. The temperature of the reaction was maintained at 37.0 C by circulation of water through a thermospacer inserted into the Beckman spectrophotometer at that temperature. The decrease in optical density (O. D.) at 340 mμ was followed at frequent intervals and for a sufficiently long period to obtain the reaction velocity during the zero order portion of the reaction. The unit is defined as a decrease in O. D. multiplied by 10^6 produced by 1 ml. of serum per minute in 3 ml. reaction mixture.[18,25]

The serum GOT activities in 77 children preceding administration of virus gave a mean value of 31 units with a standard deviation of 11 units and an upper normal limit of 60 units. The normal mean value for adults is about 20 units.[26-29] However, in many of the investigations recorded in the literature, there is no mention of temperature control of the Beckman spectrophotometer by thermospacers. In the present study it was observed that at a room temperature of 25 C, the temperature of the uncontrolled cuvette compartment was about 30 C because of the heat from the lamp. An activity of about 20 units at 30 C is equivalent to one of approximately 30 units at 37 C.[26] Consequently, it would appear that the serum transaminase activity in our group of 5-10-year-old children was not significantly different from that of adults, when corrected to 37 C. The upper limit of normal was considered as 2.5 S. D. above the mean value, i. e., 60 units.

The method for determination of GPT was essentially that described in the literature[27] with some minor modifications. The reaction mixture contained, in a final volume of 3.0 ml. and in addition to the other reactants, 0.1 ml. serum and 0.1 ml. 1,600 units LAD in albumin solution prepared freshly from an assayed stock solution of crystalline LAD in albumin. Values were corrected for blank values (usually 12 units) run with all components except serum. The mean value for a group of 29 children before administration of virus was 17 units with a standard deviation of 7 units; the upper limit of normal was 35 units. Serums with normal activity were stable in the freezer for about seven months; however, those with high activities inactivated about 20% within the first week, then remained constant for about a month, when their activity again began to decline.

The method for the determination of LAD was based on the oxidation of DPN.H by pyruvate.[25] The method has been previously described in detail.[25] The activity is expressed in units as the change in optical density per minute $\times 10^3$ effected by a concentration of 0.0167 cc. serum per cubic centimeter of reaction mixture. The normal mean value in a series of 29 apparently healthy

adults had previously been found by us to be 19 units with a standard deviation of 3.5 units. The mean value in the present study on a group of 40 children before administration of virus was 29 units with a standard deviation of 6 units. The upper limit of normal was 45 units.

The method of A. Bodansky[40] was employed for the determination of serum alkaline phosphatase. Except for the paradoxical rise of about 10%, which occurs during the first 24 hours after collection,[30] this serum enzyme retains its activity in the freezer for at least several weeks. The normal mean value in children is 7.7 Bodansky units with a mean standard deviation of 2.2 units and an upper normal limit of 13 units.[31]

The criteria for abnormality defined in the preceding sections were readily applied in most instances. The pattern of emergence of abnormal laboratory findings was practically always that of the appearance of a value significantly above the upper limit followed in a crescendo-like manner by further increases until a maximum was reached, after which the values began to decline. However, there were a few instances in which it was necessary to consider other conditions in applying the criteria. For example, a single slight but definite elevation of serum enzyme activity as, for example, that of serum PHI activity to between 80 and 100 units, occurred in a few instances early in the course of the incubation period. Unless such a value, the determination of which was usually duplicated or triplicated, was followed by a second elevated value on the subsequent determination, it was not regarded as a manifestation of hepatitis. Any single serum enzyme elevation that occurred later than 30 days after the administration of virus and was higher than the normal mean value by at least 4 S. D. was considered as possibly related to the presence of hepatitis.

Slightly elevated thymol turbidity values, that is, between 4.6 and 6.0 units, appearing occasionally early in the course of the incubation period before the 30th day, were not considered as significantly related to the disease. In a few instances, such slightly elevated values appeared singly during the 30- to 50-day incubation period, but since they were interspersed among normal or low values, they were not viewed as a manifestation of the disease. In a few cases, the thymol turbidity was elevated to about 5 to 6 units at the beginning of the incubation period; unless a sharp rise of about 2 units occurred during the 30- to 50-day period and was maintained or followed by further rises, the thymol turbidity test was not considered abnormal.

Results

Relation Between Infecting Dose and Frequency of Abnormal Clinical and Laboratory Findings.—Table 1 shows the incidence of abnormal findings during the period of 30 to 50 days following the administration of doses of 1 gm., 2 gm., and 4 gm. of the heated virus-containing material designated as WBRK No. 1 preparation. It is, of course, possible that higher doses may have produced still greater incidences than those observed at 4 gm. All findings that became manifest after 50 days were provisionally considered as due to secondary infection and are not included in Table 1. Application of the χ^2 test, *corrected for small numbers,* showed that several, but not all, of these criteria had a significantly higher incidence in the groups receiving virus than in the control group without virus. The fact that abnormal findings were present at all in the control group reflected the degree to which observations concerning jaundice and hepatomegaly might be subjective, and the extent to which these clin-

TABLE 1.—*Frequency of Abnormal Clinical and Laboratory Findings at Varying Doses of Heated Hepatitis Virus Preparation*

Dose, Gm.	No. Subjects	Per Cent of Subjects Showing					
		Fever	Jaundice	Hepatomegaly	Elevated Thymol Turbidity	Elevated Bilirubin	Elevated Serum Enzyme
0*	11	9	9	18	18	0	9
1	11	18	27	36	73 †	44 †	36
2	22	55 †	35	41	55 †	14	41
4	12	58 †	83 ‡	50	38	33	50
Total	56						

* As noted in the text, the presence of abnormal findings in this control group reflected the degree to which observations concerning jaundice and hepatomegaly might be subjective, and the extent to which these clinical findings and abnormal laboratory findings could actually occur in a population of children free of hepatitis.

† Significant at 5% level; ‡ significant at 1% level, with respect to group receiving zero dose.

ical findings and abnormal laboratory findings could actually occur in a population of children free of hepatitis. There were no significant differences among the groups receiving the various doses, except for a higher incidence of jaundice in the group receiving 4 gm. virus preparation, as compared with the group receiving 1 gm. of the preparation.

To determine whether the concurrence of several findings would yield greater significance, a value of 1.0 was assigned to the presence of each abnormal finding, and these values were totaled for each subject. The averages were 2.45, 2.45, and 3.33 for the groups that had received 1 gm., 2 gm., and 4 gm. virus preparation, respectively. Each of these was significantly higher than the value, 0.64, for the control group that had received no virus ($p \leqq 0.01$). However, there were no statistically significant differences among the three groups that had received virus.

The various laboratory and clinical criteria that have been mentioned may be found in diseases other than infectious hepatitis.[4,22,31] An attempt was made to determine whether a particular set of abnormal findings was characteristic of the groups that had received virus. Table 2 shows that the proportion of cases showing a greater number of concurrent abnormal clinical and laboratory findings increased with the dose of the virus preparation. For example, 45% of the group that did not receive virus, 91% of those that received 1 gm., 77% of those at a dose of 2 gm., and 100% of those at the 4 gm. level simultaneously had one or more abnormal findings. At the other extreme, the incidence of the concurrence of all six abnormal findings were 0, 9%, 9%, and 8% at the 0, 1, 2, and 4 gm. doses, respectively. The simultaneous occurrence of three or more abnormal findings seemed to discriminate best among the various groups; the incidences were zero in the control group, and 36%, 41%, and 58% at the respective doses. When a value of 1.0 was assigned to the occurrence of an abnormal finding in each of the children showing three or more simultaneous abnormal findings and the sums were totaled, the averages were 1.36, 1.36, and 1.92 for the groups that had received 1, 2, and 4 gm. of virus preparation, respectively. These were not statistically different from each other, but were significantly higher than the average, 0.36, for the control group that had not received virus.

The most frequently occurring abnormal findings among the 20 children with the cluster of three or more concurrent abnormal findings were elevated enzyme activity, elevated thymol turbidity, jaundice, and hepatomegaly (Table 3). However, no one couple or triad of these findings was outstandingly frequent. Since the abnormal findings also occurred alone in some children or in combination with only one other finding, the percentage incidences in those with a cluster of three or more findings varied greatly. The lowest incidence, 57%, was that for fever, whereas the highest, 95%, was for elevated enzyme activity.

TABLE 2.—*Frequency of Concurrent Abnormal Clinical and Laboratory Findings*

Dose Gm.	No. Subjects	Per Cent of Subjects Showing Concurrent Abnormal Findings: 0	1	2	3	4	5	6
0	11	55	27	18	0	0	0	0
1	11	9	36	18	9	0	18	9
2	22	23	18	18	9	5	18	0
4	12	0	25	17	8	8	33	8

TABLE 3.—*Frequency of Individual Abnormal Findings in Subjects Receiving Virus*

Criterion	Frequency in Total Group of 45 Children	Frequency in Children with 3 or More Concurrent Findings: No.	%
Fever	21	12	57
Jaundice	21	17	81
Hepatomegaly	19	17	90
Elevated thymol turbidity	27	19	70
Elevated bilirubin	12	10	83
Elevated enzyme activity	20	19	95

Relationship Between Extent of Change in Quantitatively Measurable Parameters and the Size of the Infecting Dose.—The preceding observations indicated that the occurrence of any triad of the following four abnormal findings—elevated serum enzyme activity, elevated thymol turbidity, jaundice and hepatomegaly—would constitute a firm basis for concluding that infectious hepatitis was present. The question, however, arose concerning the extent to which very mild forms of infectious hepatitis could be manifested by the presence of only one or two abnormal findings. Information bearing on this point would be elicited by determining whether there was a relationship between the magnitude of the infecting dose and the extent of change in the various parameters.

The relationship between the dose and the qualitative clinical parameters, jaundice, hepatomegaly, and fever, can only be measured in terms of frequency of occurrence. It has already been noted that these frequencies did not differ significantly from each other at 1 gm., 2 gm., or 4 gm. of the heated virus preparation, WBRK No. 1. In eliciting a relationship between these doses and the changes in the parameters capable of quantitation, that is, serum bilirubin, thymol turbidity, and serum enzymes, it has already been noted that, although it was possible to watch daily for clinical manifestations of the disease, it would not

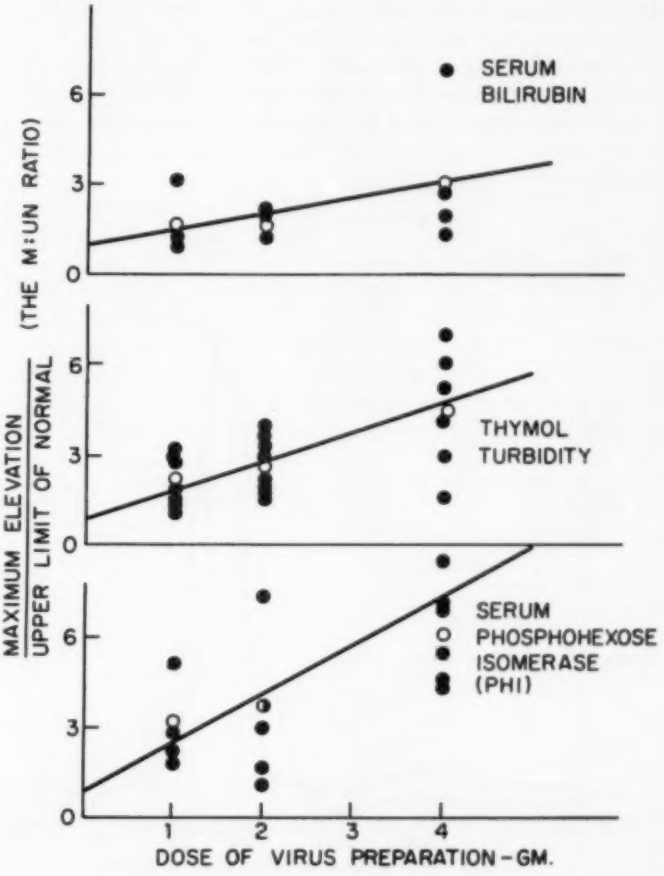

Fig. 1.—Relationship between the dose of heated hepatitis virus preparation, WBRK No. 1, and elevations in phosphohexose isomerase activity of serum (PHI), thymol turbidity, and concentration of serum bilirubin. The elevations are expressed as the ratio of the maximal elevation attained to the upper limit of the normal value of the parameter (M:UN ratio). Solid circle designates individual values for the ratio; open circle designates the mean value at the stated dose. See text for statistical evaluation.

have been warranted to draw blood each day for the performance of the biochemical and other determinations. Consequently, the time of the first appearance of an elevation in one of these quantitative parameters, or the timing of its rise to a maximal value may have been missed by several days. In spite of this intrinsic factor that might contribute variability to results, it was decided to calculate the ratios of the maximal value attained to the upper limit of normal, designated as the M:UN ratio, for these parameters in each of the subjects showing significant elevations (Fig. 1) during 30 to 50 days after administration of virus. Statistical evaluation showed that in the case of the thymol turbidity, the average value, 4.6 for the M:UN ratio at the 4 gm. dose was significantly higher than the ratio, 2.2, at the 1 gm. dose ($t=3.05$; $p=0.01$) and the ratio, 2.8, at the 2 gm. dose ($t=2.30$; $p=0.05$). In the case of the serum PHI activity, the average ratio at the 4 gm. dose was 6.2, significantly higher than the ratio, 3.1, at the 1 gm. level ($t=2.35$; $p=0.05$) and almost significantly higher than the ratio at the 2 gm. level ($t=1.94$; $p=0.08$). In contrast, the average values for the ratios of the maximum rise in bilirubin to the upper normal limit of bilirubin were 1.8 at 1 gm., 1.9 at 2 gm., and 3.2 at the 4 gm. dose level; these values were not significantly different from each other. The preceding results indicate, therefore, that the magnitudes of the rises in the thymol turbidity and serum PHI activity above normal are related to the magnitude of the dose of virus.

Comparison of Phosphohexose Isomerase and Serum Glutamic Oxaloacetic Transaminase Activities.—Serum GOT has been found by several investigators to be elevated in infectious hepatitis.[17-20] Concurrent determinations of the activities of this enzyme and the isomerase in several children receiving various doses of the virus preparation

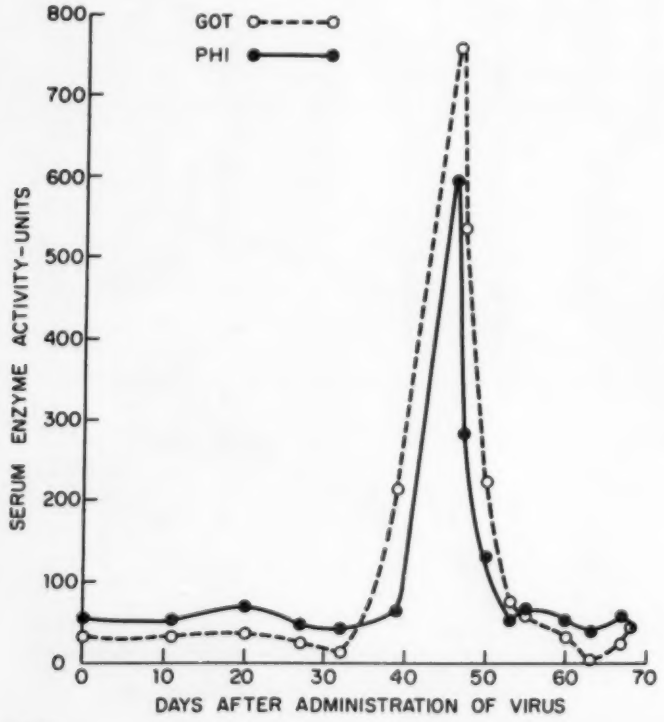

Fig. 2.—Illustrative comparison of changes in serum phosphohexose isomerase (PHI) and serum glutamic oxaloacetic transaminase (GOT) in a case (No. 1) of artificially induced infectious hepatitis.

TABLE 4.—*Comparison of Elevations in Serum Phosphohexose Isomerase (PHI) and Glutamic Oxaloacetic Transaminase (GOT) Activities Following Administration of Hepatitis Virus* *

Case No.	Day of Appearance of First Elevation		Maximum Level of Enzyme Attained		Ratio of Maximum Level to Upper Limit of Normal †	
	PHI	GOT	PHI	GOT	PHI	GOT
1	46	39	595	760	7.4	12.7
2	36	36	240	928	3.0	15.5
3	41	39	364	1,419	4.6	23.6
4	39	41	158	60	2.0	1.0
5	37	37	126	270	1.6	4.5
6	37	34	84	250	1.1	3.1

* All subjects listed received 2 gm. of virus preparation.
† The upper limit of normal (see text) was 80 units for PHI and 60 units for GOT.

showed that the rise in transaminase activity generally preceded that of isomerase and was relatively greater than the latter. This is illustrated in Figure 2. Table 4 lists six cases that had received 2 gm. of virus preparation and showed significant elevations in isomerase and/or transaminase activity; the ratios of the maximal to the upper limit of normal activities ranged from 1.1 to 7.4 and averaged 3.3 for the isomerase; for transaminase the ratios ranged from 1.0 to 23.5 and averaged 10.1. Ratios of the same high order of magnitude were also obtained in several children that had received lower doses of virus. In general, although the transaminase activities were lower than the isomerase activities during the preadministration and incubation periods, they rose to much greater levels than the isomerase during the active stage of the disease. These results would indicate that the serum GOT is more sensitive than PHI as an indicator of the presence of infectious hepatitis.

Comparison of Serum Glutamic Oxaloacetic Transaminase, Glutamic Pyruvic Transaminase, and Lactic Dehydrogenase Activities.—The human liver contains high concentrations of the transaminases [32] and lactic dehydrogenase [33] as well as of PHI.[24,33] The comparative activities of serum GOT and PHI have just been noted. Table 5 shows a comparison of the serum GOT, LAD, and GPT activities in five subjects after administration of virus and during development of hepatitis. In none of these did the rise in GPT precede that in GOT. In two of these cases, the GOT and GPT rose at the same time, and in three cases the GOT rose first. The relative rises in GPT were substantially higher than those in GOT. The ratios of the maximum level attained to the upper limit of normal ranged from 18.0 to 50.0 for the GPT ratios, as compared with a range of 10.7 to 22.7 for the GOT ratios. Figure 3 illustrates these features in greater detail in Patient 7. The GOT and GPT activities were within normal range until the 40th day. On the 45th day, both enzyme activities had risen to very high levels; on this day and as these two activities receded to the normal range,

TABLE 5.—*Comparison of Elevations of Serum Glutamic Oxaloacetic Transaminase (GOT), Glutamic Pyruvic Transaminase (GPT) and Lactic Acid Dehydrogenase (LAD) After Administration of Hepatitis Virus*

Case No.	Day of Appearance of First Elevation			Maximum Level of Enzyme Attained (Units)			Ratio of Maximum Level to Upper Limit of Normal *		
	GOT	GPT	LAD	GOT	GPT	LAD	GOT	GPT	LAD
7 †	45	45	45	1,329	1,548	74	22.2	44.0	1.6
8 †	33	35	35	759	1,748	88	12.7	50.0	2.0
9 †	34	34	N ‖	699	738	42	10.7	21.2	0.8
10 ‡	32	34	34	800	838	122	13.4	24.0	2.7
11 ‡	28	30	35	660	628	72	11.0	18.0	1.6

* Upper limits of normal were 60 units for GOT, 35 units for GPT and 45 units for LAD.
† Received 2 gm. of virus suspension.
‡ Received 0.1 gm. of an unheated virus preparation prepared from stools of three patients 25 days after experimental feeding and about 15 days before development of hepatitis.
‖ N designates no elevation.

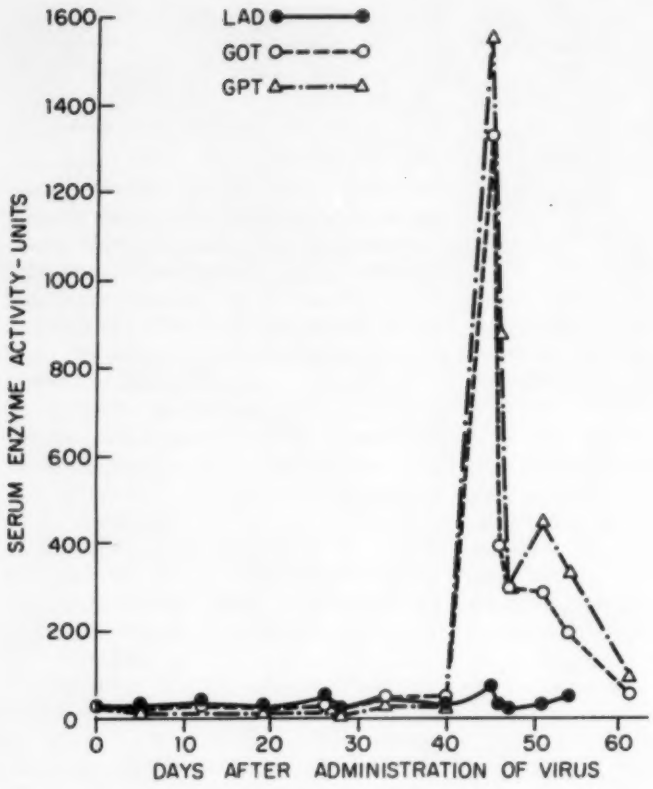

Fig. 3.—Illustrative comparison of changes in serum lactic acid dehydrogenase (LAD), glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) in a case (No. 7) of artificially induced infectious hepatitis.

the GPT level continued to exceed the GOT level. The rise in LAD was negligible. In spite of the relatively higher rises in GPT activity, it was found more practical to use GOT determinations as a guide to the development of hepatitis, since, as pointed out earlier in this paper, the GOT activity was much more stable in serum kept in the freezer.

Comparison of Serum Glutamic Oxaloacetic Transaminase and Alkaline Phosphatase.—That the serum alkaline phosphatase is elevated in infectious hepatitis has been amply demonstrated in many studies.[4] A group of 13 children received 0.1 gm. of an unheated virus suspension that had been prepared from the stools of 3 patients approximately 15 days before the onset of clinical hepatitis. Of these 13 children, 4 developed primary or secondary hepatitis. Table 6 shows, first, that in these four cases the rise in GOT preceded the rise in alkaline phosphatase and, secondly, that the relative rise was much higher. In these four cases, both enzymes returned to the normal range at about the same time.

TABLE 6.—*Comparison of Elevations of Serum Glutamic Oxaloacetic Transaminase and Serum Alkaline Phosphatase After Administration of Hepatitis Virus* *

Case No.	Day of Appearance of First Elevation		Maximum Level of Enzyme Attained		Ratio of Maximum Level to Upper Limit of Normal	
	GOT	P'ase	GOT	P'ase	GOT	P'ase
11	28	31	660	82	11.0	6.3
12	63	63	1,194	35.5	19.9	2.7
10	32	35	800	21.1	13.3	1.6
13	54	56	233	18.9	3.9	1.5

* 0.1 gm. of an unheated virus preparation obtained from stools of three patients.

TABLE 7.—*Comparison of Elevations in Thymol Turbidity (T. T.) and Serum Glutamic Oxaloacetic Transaminase (GOT) After Administration of 2 Gm. of Virus Preparation*

Case No.	Day of Appearance of First Elevation		Day of Maximal Elevation		Maximal Level Attained		Ratio of Maximal Level to Upper Limit of Normal *	
	GOT	T. T.	GOT	T. T.	GOT	T. T.	GOT	T. T.
1	39	46	46	55	760	17.8	12.7	3.96
2	36	36	36	40	928	13.6	15.5	3.02
3	39	46	46	60	1,419	8.8	23.7	1.96
6	34	N †	37	N †	250	3.7	4.2	0.82
5	37	37	41	43	270	7.7	4.5	1.71
7	45	45	45	47	1,329	8.9	22.2	1.98
14	41	41	41	47	75	10.0	1.3	2.22
8	33	40	39	47	759	17.2	12.7	3.82
9	34	40	40	54	699	15.4	11.7	3.42
Average							12.1	2.55

* Upper limit of normal GOT was 60 units, of T. T., 4.5 units.
† N designates no elevation.

Comparison of Serum Glutamic Oxaloacetic Transaminase and Thymol Turbidity Elevations.—In their study of experimentally induced infectious hepatitis in young adults, Havens and Marck [10] observed that in most of the patients who developed the disease, the cephalin flocculation test became positive relatively early, that is, in the fe-

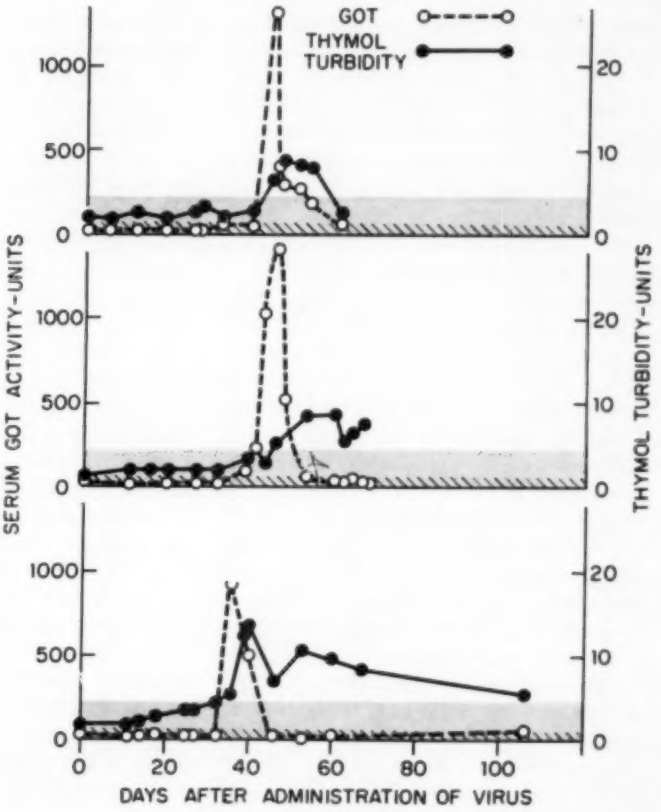

Fig. 4.—Comparison of changes in serum glutamic oxaloacetic transaminase (GOT) and thymol turbidity (T. T.) in three cases (Patients 7, 3, and 2) of artificially induced infectious hepatitis. Cross-hatched area designates normal range of transaminase activity. Lightly shaded area designates normal range of thymol turbidity.

brile, preicteric phase of the disease, and that, in general, the thymol turbidity became abnormal somewhat later. Table 7 and Figure 4 show that elevations in thymol turbidity usually occurred after the rise of the enzyme to abnormal levels and that the thymol turbidity continued to rise or was still at abnormal levels when the SGOT activity had begun to fall or had already reached normal levels. Moreover, the relative rise in the thymol turbidity as expressed by the M:UN ratio, was much less than that of the GOT.

Clinical and Laboratory Criteria in Definitive Diagnosis of Infectious Hepatitis.—The preceding studies indicate the particular set of abnormal findings required for the definitive diagnosis of infectious hepatitis, at least for the strain of virus and type of recipient used in the present study. Table 2 shows that the incidence of occurrence of single abnormal findings was approximately the same in the control group, 27%, as in the groups that had received virus, 24%. Similarly, 18% of the controls and 18% of the virus-fed groups had pairs of abnormal findings. A set of three or more abnormal findings occurred only among the group of children who had received virus. From Table 3 it may be seen that the most frequently occurring abnormal parameters in those with three or more findings were jaundice, hepatomegaly, positive thymol turbidity, and elevated serum PHI or GOT activity. The concurrence of any three or more of these should be definitive in establishing the diagnosis of infectious hepatitis.

The question arises, however, whether the presence of only one or two of the six possible abnormal findings represents a very mild or subclinical form of hepatitis. Small and transient changes in one or two parameters, similar to the changes occurring in the group of control subjects receiving no virus, were not considered as indicating the presence of hepatitis. Certainly such changes may occur in other diseases.[4] On the other hand, a substantial persistent change even in one parameter, not attributable to another condition, was provisionally regarded as a subclinical manifestation of hepatitis.

The application of this criterion of subclinical disease may now be illustrated. Subject 6 received 2 gm. of virus preparation and had no abnormal clinical or laboratory findings except a rise in the GOT from a normal value of 47 units on the 27th day after administration of virus to significantly elevated values of 155 units on the 34th day and 250 units on the 37th day. The GOT activity then receded to 160 units on the 41st day, 81 units on the 44th day, 71 units on the 45th day, and fell below the upper limit of normal, 60 units, to a normal value of 49 units on the 48th day. The rise in Subject 6, though not extreme, was substantial and was sustained during the same period of time, 8 to 10 days, as will later be shown to characterize obvious cases of hepatitis.

The interpretation of elevated thymol turbidity values accompanied by no or only one other abnormal finding during the 30- to 50-day period following administration of virus required similar detailed consideration. Elevated thymol turbidity values were the most frequent finding in children who had received virus (Table 3). However, only 70% of these elevated thymol turbidity values were present in children with three or more concurrent findings. This, together with the presence of elevated thymol turbidity values in children who had not received virus, indicated some lack of specificity in this criterion. Consequently, a thymol turbidity elevation had to be substantial and associated with some other abnormal laboratory parameter before it was considered as indicating subclinical hepatitis. For example, Patient 14, who had received 2 gm. of WBRK No. 1 preparation, showed a distinct rise from a thymol turbidity of 3.8 units on the 40th day after administration of virus to 5.2 units on the 41st day, 9.4 units on the 46th day, and 10.0 units on the 47th day. The values then began to recede, to 8.4 units on the 48th day and 7.2 units on the 54th day. This clear rise and fall, associated with a slight rise of GOT

to 75 units on the 41st day and 60 units on the 46th day was judged to indicate the development of a subclinical hepatitis in this subject.

It was now felt that the clinical and laboratory criteria, as defined in the preceding discussion, could be used in establishing fairly definitely the incidences of hepatitis due to the administration of various amounts of the virus preparation, WBRK No. 1, as well as the incidence of secondary infection. Of particular importance was the use of these criteria in assaying the possibility of the existence of the "passive-active" immunity conferred by the administration of γ-globulin. Although these clinical aspects will be discussed more fully in later reports, the data to be presented in this paper illustrate the way in which the laboratory and clinical criteria were applied to these problems.

Frequency of Primary Hepatitis at Various Dosage Levels of Virus Preparation, WBRK No. 1.—Table 8 shows the number and per cent of positive cases of primary hepatitis at various dose levels of the virus preparation. Of the 20 cases, 15 listed as positive simultaneously had jaundice, hepatomegaly, elevated thymol turbidity, and considerably elevated serum GOT or PHI activity. Two cases (5 and 22) had three of these findings. In view of the considerations we have already presented there was no question of the diagnosis in these 17 cases. Three subjects (6, 14, and 4) had what may be considered subclinical or mild forms of the disease. The reasons for making the diagnosis of subclinical hepatitis in Patients 6 and 14 have already been discussed. Patient 4 had a moderate elevation of serum PHI, 158 units, for only one day, but in view of the fact that both jaundice and hepatomegaly were present, this was considered a case of mild hepatitis.

Secondary Infection with Hepatitis.—It was noted repeatedly that the emergence of

TABLE 8.—*Positive Cases of Primary Hepatitis at Various Dosage Levels of Virus Preparation, WBRK No. 1*

	Day of Appearance of Abnormal Findings						
Case No.	Fever	Jaundice	Hepatomegaly	Elevated Thymol Turbidity	Elevated Bilirubin	Elevated Enzyme	Maximal Rise of Enzyme Activity (Units)
			0 gm.: 11 cases — none positive; 0%				
None							
			1 gm.: 11 cases — 4 positive; 36%				
15	40	49	49	42	49	42 *	234 *
16	N	45	42	42	43	39 *	184 *
17	N	40	38	39	39	35 *	148 *
18	N	51	44	42	N	46 *	416 *
			2 gm.: 22 Cases — 10 positive; 45%				
1	47	50	34	46	N	39	760
2	33	39	40	36	39	36	928
3	37	48	36	46	N	39	1,419
4	31	50	33	N	N	39 *	158 *
6	N	N	N	N	N	34	250
5	N	N	38	37	N	37	270
7	N	46	46	45	45	45	1,329
14	41	N	N	41	N	41	75
8	34	40	41	40	39	33	759
9	34	44	48	40	N	34	699
			4 gm.: 12 cases — 6 positive; 50%				
19	N	41	34	33	42	40 *	688 *
20	N	44	45	33	44	40 *	322 *
21	38	48	47	43	N	43 *	350 *
22	36	42	N	42	42	40 *	576 *
23	N	47	47	50	N	47 *	448 *
24	36	46	41	43	40	43	500 *

* PHI determinations; remainder are GOT.
N designates no abnormal finding.

laboratory and clinical manifestations of hepatitis occurred usually in groups of subjects between 30 and 50 days after administration of virus. However, in other subjects, whether given virus or acting as controls and kept in the same isolation unit with those who had received virus, the findings appeared about 60 to 70 days after administration. The gap between these two time intervals and the fact that those of the control subjects who developed hepatitis at 60 to 70 days did not do so at 30 to 50 days argued against an incubation period that varied from about 30 to 70 days. These data supported the conclusion that manifestations of hepatitis at the later period represented a secondary infection acquired at some time during the incubation period from those in whom primary hepatitis developed.

These features are well illustrated in Table 9 and Figure 5. Sixteen children were placed in an isolation unit. Ten received 0.1 gm. of an *unheated* WBRK No. 1 virus preparation, and the remaining six served as controls. Three of the ten subjects who received virus showed clear clinical and laboratory evidence of hepatitis during the 30- to 50-day period. Three developed typical hepatitis during the period 55 to 60 days after administration of virus, and the remaining three showed no manifestations of the disease during the entire observation period of about 80 days in the isolation unit. One patient showed elevated GOT values (100-200 units) before administration of virus and continued at those levels until the 66th day, when the enzyme level rose to 327 units and subsequently obtained a maximum of 850 units. His thymol turbidity also rose sharply from normal values to substantially elevated values on the 66th day. Although he had these and other clear evidence of secondary hepatitis, he was not included in Table 9 because of the high initial values for GOT.

As was to be expected, none of the six control subjects manifested hepatitis during the 30- to 50-day period. However, five of these, as Table 9 shows, developed definite clinical and laboratory evidence of the disease between about 55 and 65 days after administration of virus. Patient 38 had definite elevations of thymol turbidity and GOT activity on the 74th day. Since the preceding sample had been taken five days before, and the next sample was taken on the 84th day, it is possible that more frequent samples would have revealed other elevations. Patient 38 was designated as a

TABLE 9.—*Occurrence of Primary and Secondary Hepatitis in Group Fed Virus and Control Group Kept in the Same Isolation Unit*

Case No.	Days Under Observation	Time in Days of Appearance of Abnormal Findings: Fever	Jaundice	Hepatomegaly	Elevated T. T.	Elevated Bilirubin	Elevated GOT	Maximal Rise of GOT (Units)	Diagnosis
		0.1 Gm. Unheated Virus Preparation							
25	74	35	42	36	39	44	37	1,340	P+
26	74	40	41	52	46	49	39	850	P+
27	74	38	40	36	41	41	38	1,210	P+
28	74	33	N	N	39 *	N	35 *†	73	—
29	84	N	N	N	N	N	N	N	—
30	73	30	N	46	30 *	N	N	N	—
31	67	57	60	N	67	60	60	820	S+
32	84	N	N	26	62	N	60	860	S+
33	82	N	71	69	64	71	55	1,090	S+
20	74	N	63	60	63	63	60	1,620	S+
34	82	54	67	69	64	67	61	820	S+
35	82	48	N	36	60	N	53	256	S+
36	82	N	40	67	64	71	67	720	S+
37	74	55	60	38	60 **	60	60	1,170	S+
38	84	N	N	N	74 *†	N	74 *†	150	S±

* Slight rise. † One-day rise. ** Slight rise at 32d day. Marked rise at 64 days. N No abnormal finding. P+ Primary hepatitis. S+ Secondary hepatitis. — No hepatitis. S± Subclinical hepatitis.

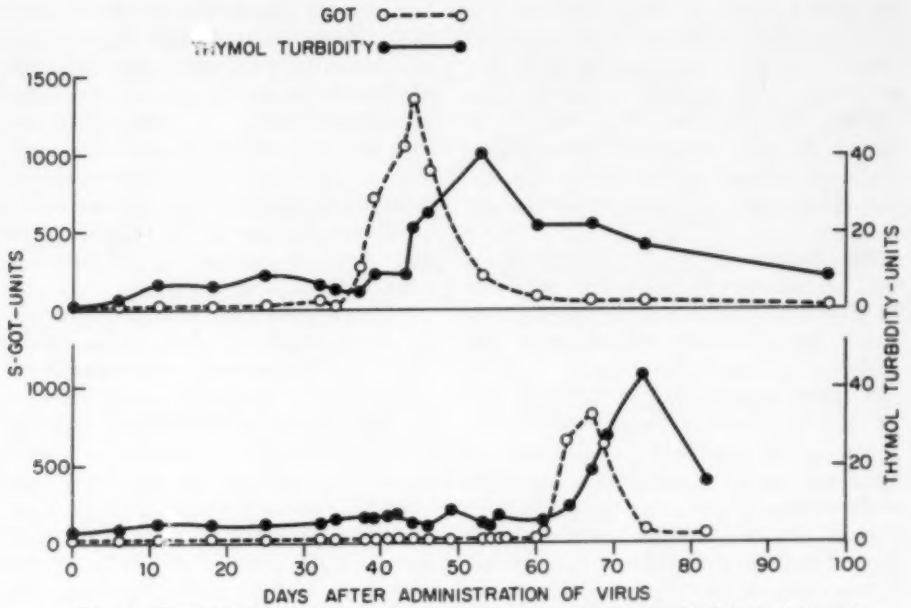

Fig. 5.—Comparison of glutamic oxaloacetic transaminase (open circles) and thymol turbidity changes (solid circles) in patient (Case 25) who received 0.1 gm. of unheated virus and contracted primary hepatitis and in control subject (Case 34) who was kept in the same isolation unit and developed secondary hepatitis.

subclinical case. Figure 5 illustrates the development and regression of the elevations in GOT and thymol turbidity values in one case (25) who had received virus and showed the typical manifestations of primary hepatitis, and in a control subject in this group who developed secondary hepatitis. The serum bilirubin also became elevated in each case. In Patient 25 it rose from normal values to 2.7 mg. per 100 cc. on the 44th day and to 10.9 mg. on the 46th day. It then receded to 3.6 mg. on the 53d day, 2.4 on the 16th day, and attained normal levels by the 67th day. In the control subject, the bilirubin did not rise until the 67th day, when the level was 3.2 mg. per 100 cc. Subsequent values were 6.7 on the 69th day, 1.1 on the 74th day, and normal, 0.5 mg. per 100 cc., on the 72d day.

Other instances of secondary hepatitis occurred in the course of these studies. As has already been noted, members of a group housed in an isolation unit who, after administration of virus, did not develop hepatitis during the 30- to 50-day period, frequently did so during the 60- to 70-day period. There was no instance of a subject developing hepatitis in both of these intervals or of a case in which the abnormal findings persisted continuously from the earlier to the later period. Of the subjects in the control group, none developed hepatitis during the 30- to 40-day period.

Use of Clinical and Laboratory Criteria of Hepatitis in Determining Effectiveness of Immunity Produced by Gamma Globulin.

The possibility of producing "passive-active" immunity was explored in two groups. Nine children served as controls, receiving 2 gm. of the heated virus preparation. The remaining 20 children received 0.06 ml. of γ-globulin per pound of body weight, followed one-half hour later by feeding of 2 gm. of the virus preparation.

Of the nine control subjects who received only virus, four (1, 2, 3, 5) developed clear evidence of hepatitis during the 30- to 50-

day period (Table 8). Two other subjects (4 and 6) have already been discussed and were considered to have subclinical or mild forms of primary hepatitis (Table 8). Two children developed secondary hepatitis at 60 and 74 days, respectively. The remaining subject showed no evidence of the disease during the observation period of about 70 days.

The findings in the 20 children treated with γ-globulin were reviewed to determine whether, in accordance with Stokes' postulate,[15] there were any combinations of laboratory findings that would indicate subclinical hepatitis during the early part of the period, namely, about 30 to 50 days following the conjoint administration of virus and γ-globulin. Only one subject had an elevation of GOT; this was to 80 units for one day and was not associated with any other abnormal laboratory findings. There were six cases with rises in thymol turbidity. In five of these the elevations were small and transitory; in the sixth instance the turbidity rose to 7.3 units on the 36th day, 9.4 units on the 39th day, receded to 6.3 units on the 41st day, and then to normal levels. Jaundice was recorded on the 47th day. During the 30- to 50-day period, fever occurred in 12 children, hepatomegaly in 3, and 3 children were judged to have jaundice. These incidences were essentially the same as those in control subjects receiving no virus (Table 1).

In this group of 20 subjects there was no combination of abnormal laboratory findings that would indicate subclinical hepatitis or, with one possible exception, any combination of abnormal laboratory and clinical findings to suggest mild hepatitis during the 30- to 50-day period following the conjoint administration of virus and γ-globulin. These results, therefore, offered no support for the thesis that the development of active immunity, if it could be induced in the manner described above, would be heralded by the early appearance of subclinical, laboratory-detectable hepatitis.

Order of Appearance of Various Abnormal Clinical and Laboratory Findings in Infectious Hepatitis.—As indicated earlier in the paper, the preceding sections have been concerned with establishing the extent to which the occurrence of abnormal values for certain clinical and laboratory parameters and the extent of change in the quantitative parameters are factors in the diagnosis of hepatitis. The present section is devoted to determining whether these abnormal findings appear in any particular order as hepatitis develops.

Eighteen of the subjects in the groups who developed primary hepatitis at the various dose levels had sequential determinations of phosphohexose isomerase activity throughout the period of observation following virus administration. It may be noted here, as has been pointed out previously, that blood for various laboratory determinations was taken at intervals of about two to seven days, usually about three days, whereas clinical observations were made daily. For example, if an enzyme activity was normal on the 39th day, and significantly elevated on the 42d day, the appearance of jaundice on the 49th day was recorded as occurring seven days later or +7; the enzyme elevation might have actually occurred any time between the 39th and 42d day. Table 10 shows time of occurrence, in days, of the various clinical and laboratory criteria preceding and following the apparent time of the rise in PHI. It may be seen that, *in general,* the occurrence of fever preceded this rise, whereas the emergence of jaundice, elevated thymol turbidity values, and elevated bilirubin followed it. Enlargement of the liver seemed to occur as frequently before the rise in PHI as after it.

Several subjects who developed primary hepatitis had sequential GOT determinations, and, in addition, some of the subjects had concurrent GOT and PHI determinations. Table 10 also lists the frequency and time of occurrence, in relation to a significant serum GOT rise, of the 13 subjects in this series who had sequential determinations of this serum enzyme. It may be seen that jaundice, hepatomegaly, elevated thymol turbidity values, and elevated

TABLE 10.—*Order of Appearance of Various Abnormal Clinical and Laboratory Findings in Infectious Hepatitis in Relation to Initial Rise in Serum Enzymes*

Criterion	Number of Positive Findings on Day *						
	−15 to −11	−10 to −6	−5 to −1	0	+1 to +5	+6 to +10	+11 to +15
A. Phosphohexose Isomerase							
Fever	0	3	7	1	0	0	0
Jaundice	0	0	1	1	11	3	1
Hepatomegaly	1	2	6	1	6	2	0
Elevated thymol turbidity	0	2	2	6	6	1	0
Elevated bilirubin	0	0	1	0	8	2	0
B. Glutamic Oxaloacetate Transaminase							
Fever	0	0	3	4	3	1	0
Jaundice	0	0	0	0	6	4	1
Hepatomegaly	0	0	4	0	4	2	2
Elevated thymol turbidity	0	0	0	4	3	6	0
Elevated bilirubin	0	0	0	1	2	4	0

* The number of days before the enzyme elevation are preceded by a minus sign, and those after by a plus sign. Findings occurring on the same day as the enzyme elevation are in the zero column.

bilirubin occurred to a preponderant degree *after* the rise in GOT. Fever occurred equally frequently before and after the rise. This "shift to the right" as compared with the distribution in relation to PHI elevations (Table 10, Part *A*) is to be expected in view of the fact that PHI elevations generally occur later than GOT elevations (Table 4).

The order of appearance of abnormal values for the clinical and laboratory criteria with respect to GOT elevations in nine cases of secondary hepatitis was essentially the same as that for the primary hepatitis except that fever, when it did occur, generally preceded the rise of GOT. There were a few instances in which hepatomegaly became evident from 16 to 34 days before the rise in enzyme.

Recession of Abnormal Findings.—It was decided to determine the duration of the various abnormal findings and the pattern that they followed in returning to normal values. Since bloods for laboratory determinations were usually taken at intervals of several days, their recorded duration, i. e., the time between the first and last abnormal values, was probably less than the actual durations. This was not the case for the clinical observations which were made daily. In several instances, the abnormal findings were still present when the subjects were discharged from the isolation unit.

The duration of abnormal findings varied greatly among the subjects with primary hepatitis. As may be seen from Table 11, the averages and ranges for the various parameters were as follows: jaundice, from 1 to 17 days, average 8 days; hepatomegaly, from 1 to 38 days, average 13 days; elevated thymol turbidity, from about 10 days to over 36 days, average 23 days; elevated bilirubin, from 2 to 20 days, average 8

TABLE 11.—*Recession of Abnormal Clinical and Laboratory Findings in Primary Hepatitis* *

	Duration in Days of					
	Jaundice	Hepatomegaly	Elevated Thymol Turbidity	Elevated Bilirubin	Elevated PHI	Elevated GOT
Range	1 to 17	1 to 38	5+ to 36+	2 to 20	1 to 17	5 to 24
Mean	8	13	23+	8	10	15

* Based on positive cases listed in Tables 8 and 9. When the parameter was normal in a particular case, that case was not included in calculating the mean values.

days; PHI, from 1 to 17 days, average 10 days; serum GOT, from 5 to 24 days, average 15 days. In general, therefore, the elevation in bilirubin was the most transient sign, and that in thymol turbidity was the most persistent. Indeed, the value given for the duration of the thymol turbidity elevation is a minimum since this was still present in many cases upon discharge from the isolation unit. It may also be seen that the duration of the GOT elevation was generally greater than the PHI elevation. No attempt was made to evaluate the recession of abnormal findings in the cases of secondary hepatitis, since there were fewer cases and since it was not possible to have as long a follow-up observation period as in the children with primary hepatitis.

Comment

It was of interest to compare the sequence of the development and recession of various clinical and laboratory manifestations of experimentally induced infectious hepatitis in the studies of the late 1940's with the observations on the comparable parameters in the present investigation. In 34 adult males who had been inoculated with virus, Neefe and Reinhold[34] found that the average times *after* the onset of disease, as marked by malaise, weakness, nausea, and fever, at which the following laboratory tests became abnormal were as follows: sulfobromophthalein retention, three days; cephalin flocculation, five days; total serum bilirubin, six days; thymol turbidity, eight days. In several adult volunteers, Drill[9] similarly noted that the elevations of serum alkaline phosphatase and bilirubin and the appearance of abnormal values for sulfobromophthalein retention and cephalin flocculation followed by several days the first clinical evidence of the disease. Havens and Marck,[10] who also studied adults, reported that the cephalin flocculation usually became positive about the fourth day of the febrile period, and the thymol turbidity about two days later. In general, jaundice began to appear within a day or two after the return of the temperature to the normal range and the liver became palpable at the same time.[3,4]

In our studies on the population of the Willowbrook State School, an abrupt clinical onset and febrile phase were not clearly discernible. Fever was not high or prolonged and its relation to other findings of hepatitis was frequently obscured by the prevalence of upper respiratory and other infections. Subjective symptoms that would ordinarily be obtainable from a normal adult population could not, of course, be elicited from the mentally deficient children. However, as may be seen from Tables 8 and 9, if the course of the disease was timed from the day of administration of virus, the pattern of appearance of the various abnormal clinical and laboratory findings paralleled in general those observed in the studies of the late 1940's.

Of particular relevance were the changes in the serum enzyme activities, parameters not available in the earlier studies of induced infectious hepatitis. The striking rise of serum GOT in hepatic disease, including infectious hepatitis, was noted by Wroblewski, Jervis, and LaDue[18] in 1956 and has since been confirmed by other investigators. As has been demonstrated in the present study (see Table 10, in particular) elevations in the serum PHI and GOT usually preceded changes in the other clinical and laboratory parameters, and the first elevation above the normal range in these enzyme activities was commonly a prelude to crescendo-like rises that reached levels 5 to 25-fold the normal levels (Table 5). The rise of transaminase frequently preceded that of isomerase. The relative rise, defined as the ratio of the maximal value to the upper limit of normal (the M:UN ratio), was greater for serum GOT than for PHI, LAD, alkaline phosphatase, serum bilirubin, or thymol turbidity. The relative rise in the pyruvic transaminase was generally greater than that of the oxaloacetic transaminase, but the rise of pyruvic transaminase did not precede that of oxaloacetic transaminase. As the former enzyme was

less stable than the oxaloacetic transaminase, it was decided not to use it as a regular criterion.

The general mechanisms underlying the elevation of serum enzyme activity have been previously considered.[35,36] When an enzyme is closely related to some tissue process, as, for example, alkaline phosphatase to osteoblastic formation or biliary obstruction, it may be expected that alteration of the level in blood will be a somewhat specific indication of deranged tissue function. On the other hand, if enzymes, such as the glycolytic enzymes and the transaminases, are involved in general cellular metabolism, the level in the blood depends on several nonspecific factors—the concentration of these enzymes in the damaged or destroyed tissue, the rate of their passage into their circulation, and their rate of removal from the circulation by excretion or metabolism. The first of these factors, namely, the relationship between the enzyme concentration in liver and its elevation in hepatitis may be briefly considered with respect to the results presented in our study.

Although data on the enzyme content of livers of children 5 to 10 years of age, such as have been considered in the present investigation, are not available, the following general comparisons may be made between the enzyme content of the adult liver and the normal serum enzyme level. Wroblewski and his associates[18,27,32] have submitted values of 142,000 for liver GOT, 18 units for the corresponding serum enzyme, 44,000 units for liver pyruvic transaminase activity, and 16 units for the corresponding serum enzyme. These figures yield a liver-serum enzyme ratio of about 8,000 for the glutamic oxaloacetic transaminase and 2,800 for the pyruvic transaminase. Bodansky[33] found that the mean value for the phosphohexose isomerase content of livers taken at autopsy from 18 patients with various types of cancer and four livers from accident cases was 29,000 units. Since the average serum level in adults in 21 units,[24] the liver-serum enzyme ratio is approximately 1,400. Analyses of nine livers from accident cases and patients with cancer yielded a mean value of 5,150 units for lactic dehydrogenase activity. The corresponding value for the serum level in adults is 19 units, and the liver-serum ratio for these enzymes, with the exception of pyruvic transaminases, paralleled the magnitude of the relative rises of these enzymes in the serum in hepatitis, and indicates that the passage from the damaged tissue to the circulation is a major factor in accounting for the magnitudes of these rises.

Of compelling interest was the manner in which various clinical and laboratory results contributed toward establishing definitively the presence of hepatitis. Although there exists in diagnosis a general tendency to regard directly perceptible data, that is, clinical findings, as of primary importance and laboratory findings as merely confirmative, the medical literature reveals instances where the converse is true. Indeed subclinical disease, whether its sequelae are ultimately serious or not, must intrinsically and by definition be that stage which is detectable only by laboratory tests. The results reported in the present study show that in infectious hepatitis in children abnormal clinical and laboratory findings are of coequal status. In the majority of instances the concurrence of at least three of the findings—jaundice, hepatomegaly, elevated thymol turbidity, and elevated serum isomerase or oxaloacetic transaminase activity—were definitive in establishing the presence of infectious hepatitis. However, there were instances in which only one or two laboratory findings, definite in their deviation from the normal range and precise in their time of occurrence after ingestion of virus, revealed the presence of subclinical disease. Moreover, as was indicated, the elevation of serum PHI and particularly GOT activity was frequently the first herald of a hepatitis that subsequently manifested itself in all its clinical and laboratory parameters.

As has already been noted, no clear evidence could be elicited in this study for the presence of a subclinical hepatitis within

the period of 30 to 50 days after the conjoint administration of virus and γ-globulin. Such a stage was postulated by Stokes and his associates [15] to exist in the production of passive-active immunity in this disease. However, it is possible that the use of different relative amounts of virus and γ-globulin, or the future development and use of more sensitive laboratory criteria may reveal the presence of such a subclinical infection in the period following the conjoint administration of gamma globulin and virus.

Summary and Conclusions

The frequency and time of appearance of abnormal clinical findings and of abnormal values for bilirubin, thymol turbidity, and various serum enzyme activities were studied in 45 children receiving various doses of a heated hepatitis virus preparation and in a control group of 11 children receiving no virus. The relationships between the dose of virus and extent of change in the quantitative, laboratory parameters were evaluated statistically.

Of a set of six criteria consisting of fever, jaundice, hepatomegaly, elevated serum bilirubin, elevated thymol turbidity, and elevated serum phosphohexose isomerase or glutamic oxaloacetic transaminase, a cluster of three or more occurred only among the groups of children who had received virus. The most frequently occurring abnormal parameters in those with three or more findings were jaundice, hepatomegaly, elevated thymol turbidity, and elevated serum phosphohexose isomerase or glutamic oxaloacetic transaminase. Of the various findings in those with a cluster of three or more abnormal findings, fever had the lowest incidence, 57%, and elevated isomerase or transaminase had the highest, 95%.

The concurrence of any three or more of the following findings—jaundice, hepatomegaly, elevated thymol turbidity, and elevated serum isomerase or transaminase—were therefore considered definitive in establishing the presence of infectious hepatitis.

A clear and substantial crescendo-like rise of one laboratory parameter occurring during a period of several days in the 30- to 50-day period after inoculation, with a subsequent return to normal levels was considered indicative of subclinical hepatitis. This indication was naturally supported by the simultaneous occurrence of an elevation in another laboratory parameter or the association with an abnormal clinical finding.

The preceding criteria were applied to the determination of the presence of hepatitis in various other groups: those receiving unheated hepatitis virus, those receiving a conjoint administration of virus and γ-globulin, and in those who were in contact with the individuals who had infectious hepatitis.

The magnitudes of the relative rise of various serum enzymes, defined as the ratio of the maximal level attained to the upper limit of normal and designated as the M:UN ratio, were, in descending order, as follows: glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, phosphohexose isomerase, alkaline phosphatase, and lactic acid dehydrogenase. The rise in the pyruvic transaminase appeared in general at the same time as the rise in the oxaloacetic transaminase, but the rise in the oxaloacetic transaminase usually preceded that in the isomerase. The serum oxaloacetic transaminase was more stable than the serum pyruvic transaminase and therefore was more serviceable as a laboratory criterion.

The rise in serum glutamic oxaloacetic transaminase generally preceded the appearance of other abnormal clinical and laboratory criteria and was, therefore, the most single useful criterion in the diagnosis of infectious hepatitis.

No clear evidence could be elicited in this study for the presence of a subclinical hepatitis within the period of 30 to 50 days after the conjoint administration of hepatitis virus and γ-globulin.

We are indebted to Dr. Paul H. Hoch, New York State Commissioner of Mental Hygiene, and to Dr. Harold H. Berman, Director of the Willowbrook State School, for their cooperation. We also acknowledge the statistical advice of Dr. Irwin D. J. Bross and the technical assistance of Miss Cass Fanning, Miss Anita Smith, Mrs. Charlotte Wilson, and Miss Tina Marmorale.

410 E. 68th St. (21)

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Effect of Dietary Supplement of Nonfat Milk on Human Growth Failure

Comparative Response in Undernourished Children and In Undernourished Adolescents

TOM D. SPIES, M.D.; SAMUEL DREIZEN, D.D.S., M.D., Chicago; RICHARD M. SNODGRASSE, Ph.D., Philadelphia; CLEO M. ARNETT, M.S., and HAMILTON WEBB-PEPLOE, Birmingham, Ala.

Qualitative and quantitative disturbances in skeletal and somatic growth of children ingesting nutritionally inadequate and unbalanced diets have been described in previous publications from this Clinic.[1-5] The nutritive inadequacies, while rarely severe enough to cause clinical lesions, result in an insidious and progressive type of growth failure detectable on the Wetzel grid and in roentgenograms of the hand and wrist. The measurable manifestations are largely corrected by the addition of milk supplements to the substandard home diets. The remedial effects of the milk supplements are only apparent when the amount given and the duration of supplementation is sufficient to alleviate the bulk of the nutritional deficit. The responsiveness of nutritive and growth failure to milk supplements has been demonstrated under completely unregimented conditions, the only controlled factor being the supplement per se.

Submitted for publication Dec. 14, 1958.

Northwestern University studies in nutrition at the Jefferson-Hillman Hospital, Birmingham, Ala. From the Department of Nutrition and Metabolism, Northwestern University. These studies were supported by grants from the Birmingham Citizens Committee Fund and the Fuller E. Callaway Foundation.

Professor of Nutrition and Metabolism, Northwestern University Medical School (Dr. Spies). Assistant Professor of Nutrition and Metabolism, Northwestern University Medical School (Dr. Dreizen). Professor of Anatomy, Temple University, School of Dentistry (Dr. Snodgrasse). Dietitian, Nutrition Clinic, Hillman Hospital (Miss Arnett). Research Technician, Nutrition Clinic, Hillman Hospital (Mrs. Webb-Peploe).

These studies were confined to prepubescent children. In a recent report from this Clinic, it was shown that prolonged nutritive failure throughout childhood and adolescence delays epiphyseal closure in the long bones.[6] Thus, protracted undernutrition would appear to prolong the growth period by retarding the attainment of skeletal maturity. Whether skeletal retardation in adolescence can be completely relieved by dietary means is uncertain. To determine whether it is feasible, the studies of the human growth promoting properties of nonfat dry milk have been extended to compare the response in undernourished children and in undernourished adolescents.

Materials and Methods

Selection of Subjects.—The growth study series of the Nutrition Clinic was screened for children with retarded skeletal and developmental age. Skeletal age was determined from roentgenograms of the hand skeleton by the Todd inspectional method[7] using the Greulich-Pyle Atlas as the standard of reference.[8] Developmental age was obtained by projecting horizontally the isodevelopmental level reached by the subject and noting the age at which the projection crossed the 67% standard auxodrome on the Wetzel grid.[9]

Only children with a personal and familial history of undernutrition and freedom from food allergies and non-nutritional diseases were considered. Final selection was based on the accessibility of the home and cooperative attitude of the parents and child. Twenty subjects (ten boys and ten girls) who met each of the criteria were chosen to receive the supplement. Ten ranged in age from 4 years 3 months to 12 years 6 months, and ten from 15 years 3 months to 16 years 7 months. Each member of the latter group had

Nutrient Value of Nonfat Dry Milk as Determined by Direct Analysis
(Quantities per 100 Gm.)
(Carbohydrate, 51.40%; Protein, 34.20%; Ash, 7.58%; Moisture, 5.91%; Fat, 0.65%; Fiber, 0.26%)

Amino Acids	Gm.	Minerals	Mg.	Vitamins and Essential Fatty Acids	Amount
Alanine	1.20	Calcium	1,530.0	Vitamin A	243 U. S. P. units
Arginine	1.66	Cobalt	0.002	Thiamine	0.432 mg.
Aspartic acid	1.73	Copper	0.11	Riboflavin	1.90 mg.
Cystine	0.38	Iodine	0.46	Niacin	1.73 mg.
Glutamic acid	4.57	Iron	0.74	Vitamin B_6	0.38 mg.
Glycine	0.62	Magnesium	100.0	Pantothenic acid	2.58 mg.
Histidine	0.96	Manganese	0.06	Vitamin B_{12}	0.00106 mg.
Isoleucine	2.55	Phosphorus	1,120.0	Folic acid	0.0031 mg.
Leucine	3.63	Potassium	1,530.0	Choline	19.7 mg.
Lysine	3.20	Sodium	514.0	Biotin	0.012 mg.
Methionine	1.34	Zinc	1.5	Inositol	80.3 mg.
Phenylalanine	1.67			p-Aminobenzoic acid	0.01 mg.
Proline	3.07			Vitamin C	7.56 mg.
Serine	2.26			Vitamin D	50 U. S. P. units
Threonine	1.51			Linoleic acid	340.6 mg.
Tyrosine	1.67			Linolenic acid	4.42 mg.
Tryptophane	0.42			Arachidonic acid	0.325 mg.
Valine	2.73				

roentgenographic evidence of delayed epiphyseal fusion. All were white, of British ancestry, and natives of north-central Alabama.

Method of Study.—Each subject was followed through a presupplement, supplement, and postsupplement period of six months' duration. Growth progress was assessed from height, weight, and chronological age measurements plotted on the Wetzel grid [9] and from analyses of serial roentgenograms of the left hand and wrist. These data were collected at intervals of three months. The skeletal and developmental age gains in each phase were determined and individual and group comparisons made.

The daily supplement consisted of 6 oz. of "Carnation Instant Nonfat Dry Milk" sweetened with 0.5 oz. granulated sugar, flavored with 7 ml. imitation vanilla flavor, and suspended in water sufficient to make 433 gm. The nutrient value of the supplement determined by chemical and biological assay is shown in the Table. The supplement was administered under the supervision of personnel of the Nutrition Clinic either at home or at school six days per week for six months. The time of administration was scheduled to avoid interference with regular meals. When part or all of the supplement was not consumed, regardless of reason, the remainder was returned to the Clinic, weighed, and subtracted from the daily quota. A quantity equal to that returned was reoffered on a subsequent visit. The mean amount of supplement consumed by the preadolescent group was 91% of that offered; by the adolescent group, 98%.

The nutritional value of the diet with and without the supplement was estimated from records of all the foods eaten, including the school lunch, for three consecutive days each month. A staff dietitian personally observed the type and grade of food purchased, methods of preparation, and the size of the portions served. From these records the average daily intake of nutrients was calculated and contrasted with the daily allowances recommended by the National Research Council. No nutritional or medical guidance was given, nor were any alterations made in the regular habits or dietary practices of any of the subjects throughout the course of the study.

The biological value of the milk supplement was determined further in a group of 150 young Sprague-Dawley male rats. Five groups, each containing 30 animals, were given the following diets ad libitum beginning at 6 weeks of age:

Group I: Basic diet derived from food staples consumed by endemic pellagrins in north-central Alabama. This diet contained 18% lard, 19% granulated sugar, 35% unenriched degerminated white corn meal, and 28% unenriched white wheat flour.

Group II: Basic diet in which niacin, riboflavin, thiamine, and iron enriched corn meal and wheat flour were substituted for the unenriched forms. This diet was representative of the basic foods consumed by the children included in this study.

Group III: Basic diet containing enriched corn meal and flour plus nonfat dry milk in the proportion ingested by the children during the supplementation period.

Group IV: Basic diet with enriched corn meal and wheat flour plus nonfat dry milk plus equivalent of a school lunch, all reduced to the ratios consumed by the school age children during the period of supplementation. The school lunch equivalent contained 9% cooked lean beef, 19% canned chopped turnip greens, 1% white potatoes,

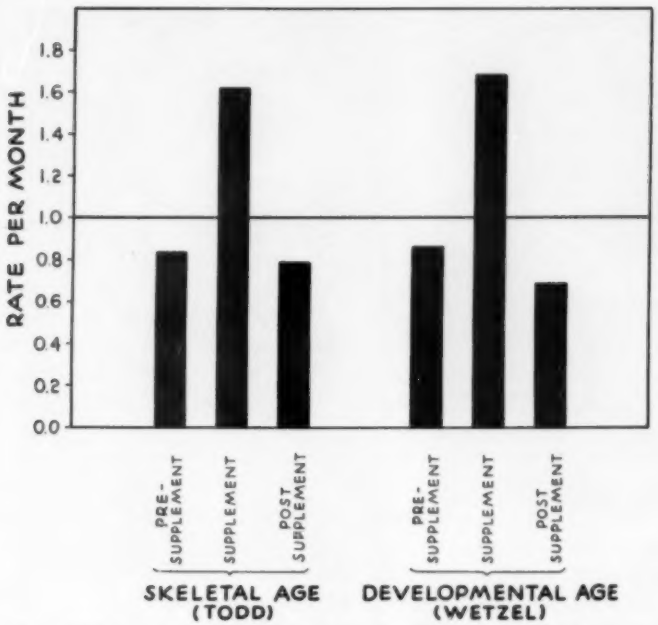

Fig. 1.—Effect of milk supplements on skeletal and somatic growth of 10 undernourished children.

4% enriched bread, and 5% butter. (Nonfat milk 4% and butter 2% were substituted for the whole milk contained in school lunch.)

Group V: Stock diet containing all of the known nutritional essentials for the rat.

The rats were weighed every week, x-rayed every three months, and necropsied at the end of six months. Histologic sections stained with eosin and hematoxylin were prepared and examined microscopically to ascertain the effects of the added

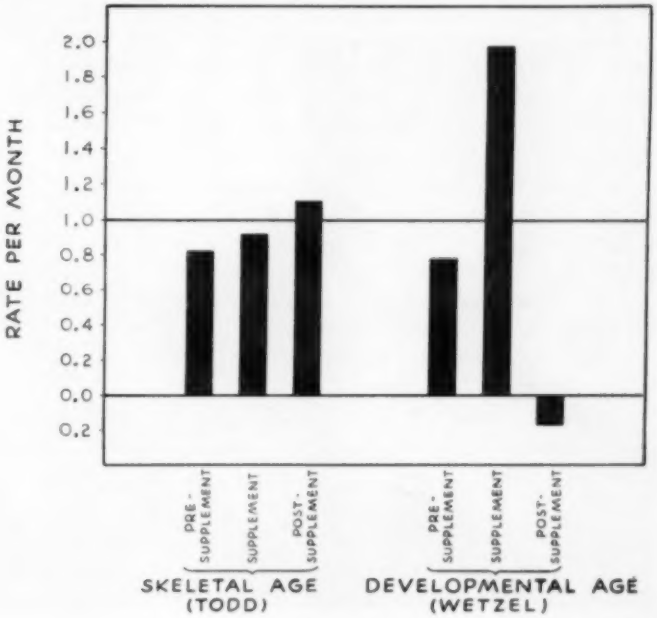

Fig. 2.—Effect of milk supplements on skeletal and somatic growth of 10 undernourished adolescents.

milk on the skeletal and somatic growth of the rats in each group.

Observations

The respective group gains in skeletal and developmental age during each of the three phases are shown in Figures 1 and 2. In the *preadolescent* group (Figure 1), the mean monthly increments in developmental age were 0.86 in the presupplement period, 1.68 in the supplement period, and 0.86 in the postsupplement period. The corresponding mean monthly skeletal age gains were 0.83, 1.62, and 0.79 respectively. The differences in the mean skeletal and developmental age rates between the presupplement and supplement period and between the supplement and postsupplement period were statistically significant. For developmental age, the *t* ratio* for the supplement and presupplement means was 4.58; for the supplement and postsupplement means, 5.04. The respective *t* ratios for skeletal age were 4.12 and 3.67. The differences in the mean rates between the pre- and postsupplement periods were not statistically significant (*t* ratio for skeletal age, 0.21; *t* ratio for developmental age, 1.21).

At the beginning of supplementation, the mean lag in developmental age was 15.2 months (range 4 to 27 months); in skeletal age, 21.5 months (range 14 to 31 months). Mean gains in developmental age of 10.1 months and in skeletal age of 9.9 months during the supplement period reduced the deficits by 27.0% and 18.1% respectively. As a group, the preadolescent children showed a mean increase of 95.3% in developmental age rate and 96.4% in skeletal age rate while receiving the milk supplements. In the postsupplement period, the mean developmental and skeletal age gains receded to 79.1% and 95.2% of the presupplement values.

The mean weight gain during supplementation was 4.7 lb. (range 2.00 to 8.75 lb.); the mean height increase, 1.5 in. (range 1.18 to 1.89 in.). Individually, each of the 10 preadolescent children equaled or exceeded the standard rates of increase in skeletal and somatic growth during the supplementation period. Although the group values for the period were of the same order of magnitude, there was no correlation between individual gains in skeletal and developmental age (coefficient of correlation −0.183). Representative of the growth response made by the preadolescent children is that of the girl shown in Figure A, who gained 6.5 lb. and 1.25 in. during the six-month period of supplementation.

The collective gains in developmental and skeletal age made by the *adolescent* group before, during, and after supplementation are presented in Figure 2. In the presupplement period, the mean monthly rates of increase in developmental and skeletal age were 0.78 and 0.82 respectively; in the supplement period, 1.98 and 0.92, and in the postsupplement period, −0.17 and 1.10. The differences in mean developmental age rates between the presupplement and supplement periods and between the supplement and postsupplement periods were statistically significant (*t* ratio 4.53 and 7.94 respectively) whereas those for skeletal age were not significant (*t* ratio 0.96 and 2.07 respectively).

Prior to supplementation, the mean lag in developmental age among the adolescents was 13.1 months (range 4 to 35 months); in skeletal age, 11.9 months (range 1 to 21 months). After supplementation, the mean developmental age lag decreased to 7.6 months, a reduction of 45.3%, and the mean skeletal age lag increased to 13.3 months, a rise of 20.1%. The mean weight increase while the subjects were receiving the added milk was 12.31 lb. (range 8.3 to 15.9 lb.); the mean height gain, 1.04 in. (range 0.59 to 1.97 in.). In the postsupplement period there was a mean weight loss of 1.47 lb. (range −6.0 to +4.6 lb.)

* t ratio = $\frac{\text{actual difference between means}}{\text{standard error of difference between means}}$. In the *t* table, for a sample size of 10 children, the 1% confidence limit is 3.250 and the 5% confidence limit is 2.262.

Fig. A.—Girl before supplementation (left) and after six months of milk supplement, during which she gained 6.5 lb. and 1.25 in. (right).

Fig. B.—Appearance at 26 weeks of age of rats given basic diet (Group I) and basic diet plus nonfat dry milk (Group III).

Fig. C.—Comparison of eyes of rats fed basic diet (left) and basic diet plus nonfat dry milk (right).

Fig. D.—Osteoporosis and retarded growth in mandible of rat fed basic diet (left) contrasted well-mineralized mandible of rat fed basic diet plus nonfat dry milk (right).

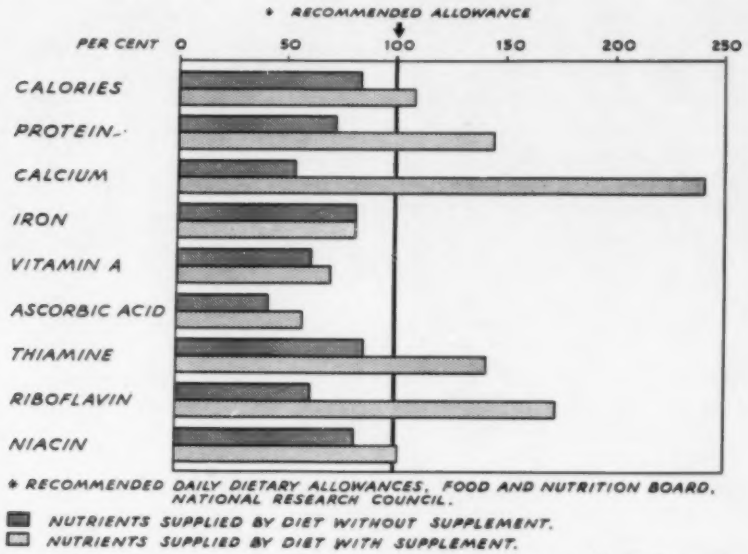

Fig. 3.—Relative proportion of nutrients supplied by regular diet and by milk supplement in 10 children.

and a mean height gain of 0.46 in. (range 0.0 to 1.02 in.). In each member of the adolescent group the developmental age gain during the supplement period was accelerated to an extent which exceeded the standard rate of one developmental age month per calendar month. Six of the ten showed a concomitant increase in the rate of skeletal maturation during this period, while four showed a decrease. The gains in skeletal age were substantially lower than in developmental age, with only 5 of the 10 subjects progressing at a rate which equaled or exceeded one skeletal age month per cal-

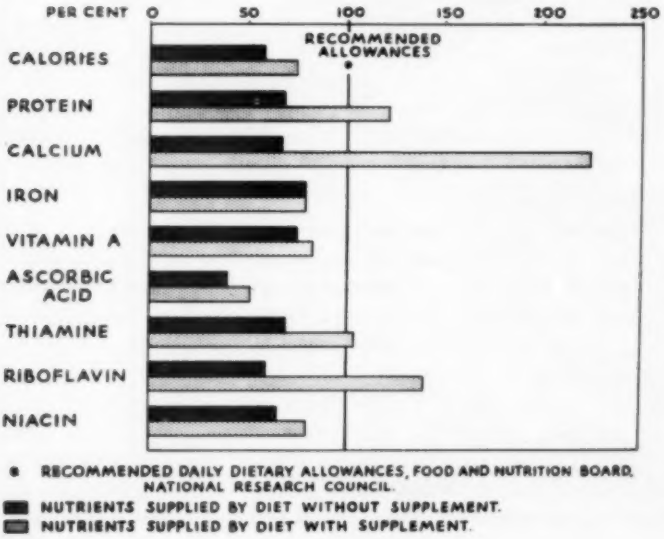

Fig. 4.—Relative proportion of nutrients supplied by regular diet and by milk supplement in 10 undernourished adolescent children.

endar month. There was no significant correlation between the individual increases in developmental and skeletal age while the subjects were receiving the supplement (coefficient of correlation −0.271). In no subject did the addition of the milk supplement to the daily diet produce a noticeable reduction in the delay in fusion between the shafts and epiphyses in the hand and wrist. Eight of the ten subjects lost weight during the postsupplement period and three failed to undergo any further increase in height.

The proportion of nutrients supplied by the regular diet and by the added milk in each group is depicted in Figures 3 and 4. In neither group did the home diets meet the daily recommended allowances for any of the nutrients for which standards have been accepted. The diets of the adolescents were inferior to those of the preadolescents in all nutrients except calcium and vitamin A. The added milk satisfied the daily requirements for age and sex for calories, protein, calcium, thiamin, riboflavin, and niacin in the preadolescent children and for protein, calcium, thiamin, and riboflavin in the adolescent group. The contribution of iron, vitamin A, and vitamin C by the supplement was negligible.

There was a striking response of the young white rats to the nonfat dry milk (Fig. 5). Those on the basic diet with or without enriched corn meal and wheat flour (Groups I and II) developed a deficiency syndrome characterized grossly by dacryohemorrhea, alopecia, priapism, testicular atrophy, and stunted growth (Figs. B and C). The significant microscopic changes were fatty metamorphosis of the liver (Fig. 6); osteoporosis (Fig. D); atrophy of subcutaneous tissue and muscles; and arrested spermatogenesis, chondrogenesis, and osteogenesis. In contrast, the groups given the added milk (Groups III and IV) showed no gross or microscopic evidence of the deficiency manifestations. The group given the dry milk and the equivalent of a

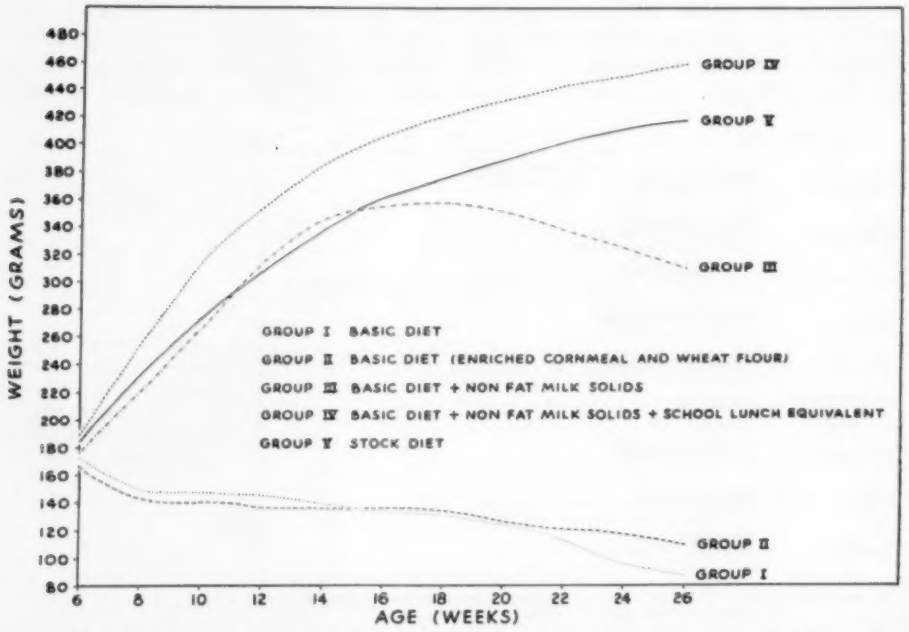

Fig. 5.—Response of young white male rats to experimental diets as measured by changes in body weight.

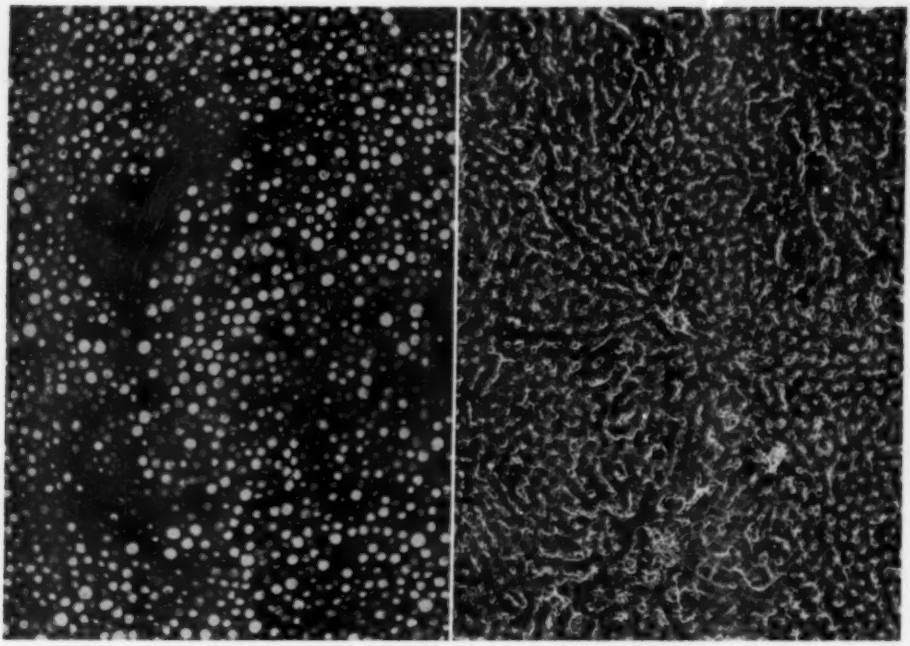

Fig. 6.—Prevention of fatty metamorphosis in liver of rats by nonfat milk. Basic diet (left). Basic diet plus nonfat milk (right).

school lunch (Group IV) had weight gains considerably in excess of the group receiving the stock diet (Group V). Those given the dry milk without the school lunch equivalent (Group III) failed to attain the size reached by the rats on the stock diet (Group V). Roentgenographically (Fig. D), the bones of the rats given the added milk (Groups III and IV) were much more heavily mineralized than those on the stock diet (Group V).

Comment

The statistically significant increase in the rates of skeletal and somatic growth in the preadolescent children during the period of supplementation and the reversion of these rates to the presupplement values when the supplement was terminated indicates that the cumulative growth lag in young undernourished children is reversible when suitable additions are made to the diet. The growth response in this group was similar in magnitude to that observed in a series of undernourished prepubescent children [10] given the same amount of nonfat dry milk for a six-month period in 1952. Failure to remove the entire growth debt may be attributable to the persistent uncorrected deficiencies of such growth factors as iron, vitamin A, and vitamin C. This is substantiated by the rat experiments which showed a notable difference in somatic growth between the animals given the added milk and those given added milk plus the equivalent of a school lunch comprised of lean beef, butter, enriched white bread, chopped turnip greens, and potatoes. The detectable increase in growth rate in the preadolescent children despite the prevailing dietary deficiencies underscores the importance of calories and high-quality protein in alleviating to a significant extent the growth failure stemming from a generally deficient diet.

In the preadolescent group, the milk supplement promoted growth in both the hard

and soft tissues to a similar degree. There was no significant correlation, however, between individual gains in skeletal and general body growth, suggesting that the supplement was utilized by each subject in a distinctive manner. The magnitude of the growth response was not related to the degree of retardation present prior to the period of supplementation, again denoting an individuality of performance.

The variation in the specificity of the growth response to the milk supplements was especially noteworthy in the adolescent group. Collectively this group underwent a statistically significant acceleration in rate of general body growth without a concurrent discernible increase in rate of skeletal maturation. The bone response was confined almost exclusively to size, maturation being relatively unaffected. The resultant increase in height in this group could not have been accomplished had skeletal maturation been hastened to the point of fusion. The lack of a measurable increase in rate of skeletal maturation in the adolescent group during the period of supplementation accords with Todd's[7] observation that if inhibition of progress in skeletal maturation is sufficiently great during the preschool period as to be apparent, the chances of restoration during adolescence are very slight. The present findings indicate that with increasing age children become increasingly less susceptible to the influences that disrupt the normal process of skeletal maturation but retain their susceptibility to those that affect dimensional growth.

Summary and Conclusions

The effectiveness of nonfat dry milk in alleviating growth failure was studied in 10 undernourished preadolescent and in 10 undernourished adolescent subjects. The skeletal and somatic growth progress of each subject was followed through presupplement, supplement, and postsupplement periods, each of six months' duration. The nutrient value of the supplement (given six days per week for six months) was approximately equivalent to that of 2 qt. of skim milk. It was observed that

1. In the preadolescent group the added milk induced a statistically significant acceleration in skeletal and general body growth which was not maintained after the supplement was terminated.

2. In the adolescent group there was a statistically significant increase in rate of general body growth during the period of supplementation without a significant change in the rate of skeletal maturation.

3. There was no significant correlation between individual gains in skeletal and somatic growth in either group during the supplement period, each subject reacting to the added milk in his own distinctive manner.

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The Development of Ten Children with Blindness as a Result of Retrolental Fibroplasia

A Four-Year Longitudinal Study

ARTHUR H. PARMELEE Jr., M.D.; CLAUDE E. FISKE, Ph.D., and ROGERS H. WRIGHT, Ph.D., Los Angeles

It is well known that many children who are blind from birth or early infancy have normal intelligence, make adequate social adjustments and are successful in school.[1-3] These children ultimately lead constructive, independent, happy adult lives. There are successful teachers, chemists, physicists, doctors, psychologists, entertainers, and businessmen, as well as housewives, who are blind.[4]

The parent who is faced with the problem of rearing a blind infant has a difficult task. The emotional reaction of most adults to the handicap of blindness is very great.[5,6] We, as a society are highly visually oriented, witness the growth of the television industry. Society does not readily accept a blind person. The parent of a blind infant has all of these feelings plus the feelings of being in some way responsible for the child's blindness. Such a parent, therefore, finds that he has to cope with these intense emotional feelings of his own before he can be effectively emotionally available to the infant. The blind infant, of course, needs the same emotional support and rich interplay of emotional life with his parents that all infants need for the development of a socially adequate personality. Furthermore, bereft of one important sense the blind child needs additional stimulation in other sensory areas rather than the social and sensory isolation he often encounters.

As any child progresses through infancy and childhood, parents are constantly looking for evidence that the child is doing well. The parents of most children make unconscious and conscious comparisons between the progress of behavior in their own child and the children they see around them, or have known in the past. They gain confidence as each milestone of development is successfully passed.

The parent of a handicapped infant, in this instance a blind infant, usually has had no experience with the development of such infants and children, and hence no way to judge successes or failures. These parents are afraid to rely on the usual cues on how to proceed with child rearing. A particular problem for them is how and when to urge the child to independent activities and self-help. Therefore, the parents turn to doctors and other professions for authoritative advice.

There are blind children who have serious neurological disorders, including mental deficiency.[8] It is important for the parents to know when this is the case so that they do not drive themselves and their child to distraction seeking to achieve an impossible goal. On the other hand, sometimes a blind child appears seriously mentally retarded because of major emotional problems and after psychiatric help he evidences normal intelluctual potential. The recognition of these children early is critical.

The problem of evaluating the developmental progress of the child with blindness as a result of retrolental fibroplasia is further complicated by the fact that this condition develops primarily in small, premature infants weighing less than 1,800 gm.

Submitted for publication Dec. 10, 1958.

Aided in part by a grant from the American Foundation for the Blind.

That the developmental progress of premature infants is delayed to the extent of the number of weeks of prematurity is known.[7] Unless this is understood, any premature infant may be judged as retarded in development in early infancy. However, it is also known that there is a higher incidence of neurological disorders and mental retardation in small, premature infants than among full-term infants.[8,9] Furthermore, significant emotional behavioral disturbances may be more frequent in premature infants than in full-term infants.[9,10] All of these factors increase the urgency for adequate information about the development of blind premature infants to aid all who work with the blind children in making as accurate evaluations as possible.

Gesell [7] has stated that his child development norms for term infants can be applied to premature infants, if one corrects the infant's age by the number of weeks of prematurity. He further states that blind infants follow essentially the same developmental patterns as infants with vision. Thus, at least during the first year of life, the Gesell developmental test should be applicable to blind premature infants, allowing for the weeks of prematurity. In order to test this concept, in the fall of 1954 10 prematurely born infants of less than 1 year of age who were blind as the result of retrolental fibroplasia were tested, using the Gesell infant test.[7] These infants were considered by workers for the Field Service for Blind Preschool Children of the California School for the Blind to be normal insofar as they could determine from observations in the home. These infants were compared with 10 prematurely born infants with normal vision who were similarly tested and also 80 full-term infants. All of the infants were tested by the same examiner (A. H. P.). There was no statistical difference in the mean score for all three groups. It appeared that the statements made by Gesell were substantiated. These findings were reported [11] in 1955.

Although there is evidence that developmental quotients as obtained by infant tests do not correlate significantly with intelligence quotients obtained in later years by standard tests,[12-14] especially the Stanford-Binet test, these studies have generally included only children with average or higher intelligence. It is accepted by some that children with significant mental impairment can be detected by infant tests. Furthermore, this type of testing is more effective in detecting neurological disorders in infants than the standard neurological examination as applied to adults.[15]

All of the 10 prematurely born infants blind as the result of retrolental fibroplasia were judged to be developmentally and neurologically normal, except 1. This child (Case 8) was judged to be developmentally normal, but was found to have a major degree of hearing loss bilaterally and some ataxia as manifest by his poor balance and

TABLE 1.—*Comparison of Early Infant Developmental Test Results and Later Intelligence Testing of the Prematurely Born Infants with Normal Vision*

			Original Developmental Examination		Retesting		
Case No.	Weeks of Prematurity	Birth Wt., Lb. — Oz.	Chronological Age in Weeks at Time of Test	Developmental Quotient	Chronological Age at Time of Retest	Stanford-Binet Score	Vineland Score
1	13	2	42	96	5 yr. 2 mo.	93	110
2	8	3 — 9	32	100	3 yr.	76	91
3	6	3 — 15	22	112	4 yr. 9 mo.	100	82
4	5	4 — 6	26	123		Not available	
5	4	4 — 11	18	107		Not available	
6	4	4 — 15	20	100	5 yr. 3 mo.	104	106
7	4	5	33	113		Not available	
8	4	5	28	108	3 yr. 2 mo.	102	
9	4	5 — 2	33	110	5 yr. 4 mo.	114	109
10	3	4 — 6	26	121	6 yr. 2 mo.	116	108

TABLE 2.—*Results of the Psychological Tests and Other Evaluations of the Blind Prematurely Born Children*

Case No.	Weeks of Prematurity	Birth Wt.	First			Second	Third		Fourth	
			Age in Weeks	Gesell Test Dev. Quot.	Age in Months	Play Evaluation and Parent Interview	Age, Yr. & Mo.	Psychological Testing	Age, Yr. & Mo.	Final General Evaluation from Observations and Biographical Material
1	12	2 lb.	27	100	25	Exploration of the toys very limited; walked holding onto furniture and explored room; mother had difficulty reaching him verbally; seems to be withdrawn, and emotional problems may be contributing to poor behavioral functioning	2- 5 4	Vineland 54 Vineland 66	4	Retarded behavioral development primarily on basis of emotional disturbance; intellectual potential probably near normal; family accepting psychiatric help; general health good; no vision
2	12	2 lb. 3 oz.	39½	116	26	His walking, exploration of the room and of the toys impressive; biggest lack was language; normal mentality still seemed probable; emotional conflict with parents evident	2- 9 3-10	Hayes-Binet Estim. 104 Vineland 50	4- 4	Retarded behavioral development seems to be largely on an emotional basis; psychiatric help is in progress; average intellectual and social development expected; general health good; no vision
3	10	2 lb. 3 oz.	53	102	38	Exploration of the toys limited though initially she seemed interested; talked to herself in jargon of her own; ignored people around her; poor behavioral function may be on basis of emotional withdrawal	4- 7	Vineland 64	5- 3	Normal early development suggests basically normal potential; regression after 2 years of age was associated with eye pain, surgery, and family difficulties; emotional factors seem dominant; psychiatric help not accepted; general health fair; no vision
4	8	2 lb. 7 oz.	47	94	25	Walked well; talked in short phrases and had an estimated 100 word vocabulary; interest in people and social situations good; considered mentally and socially normal	2-10	Hayes-Binet 97 Vineland 81	4- 5	Mentally and socially normal; takes care of own needs; anticipated she will attend a regular kindergarten; general health is good; no vision in right eye; sees large objects held close to left eye
5	11	2 lb. 10 oz.	53	100	29	Her play was extremely complex; could catch a ball; adapt to reversal of the form board with few errors; conversation expansive; gave her full name and correctly identified herself as a little girl; no question about her good mental and social development	3- 1	W. I. S. C. 123+ Vineland 122	4- 8	She continues to be mentally and socially advanced; present emotional problems mild and realistically related to her father's serious illness; should do well in an integrated school program; general health good; no vision

6	8	2 lb. 12 oz.	41	103	32	She had enough vision in her left eye that she could identify and name objects in a picture; performed at a 30-34-month level on the Gesell scale and was given a developmental quotient of 100; language and social behavior suggested potential better than this	2- 9	Hayes-Binet 97 Vineland 120	4- 5	This child impresses one as a charming, confident, friendly, intelligent girl; uses the vision in her left eye so well that her behavior is like that of a sighted child; will enter regular kindergarten and may learn to read large print in sight-saving classes later; will probably also need Braille
7	13	2 lb. 12 oz.	43	106	18	She explored the toys fully and played a game with the ball; walked all around the room with two hands held; vocalized a complicated jargon and echoed words; was considered mentally and socially normal	5- 4	Hayes-Binet 131 Maxfield-Bucholz 92	5-10	This child is doing very well in a regular school for sighted children and a special Braille program; rides a two-wheeled bicycle, ice skates and roller skates; favorite sport is fishing; general health good; no vision
8	12	3 lb. 3 oz.	47	100	17	Wears hearing aid but no observable change; may make more sounds; explores toys primarily by tapping them against his teeth or head; rubs his body and hands against large objects; ingenuity in use of tactual sensory experiences suggested a good mental potential	2-10	Vineland 33 Direct testing not possible	4- 6	General progress has been good; feeds himself and is toilet trained; is easily disciplined; interested in people and his environment; most delayed in speech development because of his severe hearing loss bilaterally; has useful though very limited vision in his right eye and none in his left eye; at present attends a play school for cerebral palsied children and has speech instruction
					23	Walks alone; feeds self with fingers; vision in right eye useful and can see objects held close to the eye; very interested in everything in his environment; mental potential still considered good	3-11	Vineland 50 Direct testing not possible		
9	9	3 lb. 6 oz.	42.5	104	22	Walked rapidly, using her vision to guide her; said many words in Spanish and some in English; on request would point to parts of her body without error; considered to have normal potential	4- 7	Hayes-Binet 82 (Examiner felt score lowered by apprehension of child) Vineland 98	6- 3	She is in the first grade of a parochial school; can read the regular primers and copies written material; speaks Spanish and English well; walks to school alone; prognosis is good; though she has a severe visual handicap, she is not "blind"; with glasses and using both eyes vision is 10/70
10	10	3 lb. 8 oz.	25	100	22	Walked holding on; vocabulary 20 words; manipulation and exploration of the toys good; no vision at all; considered to be doing well mentally and socially	2- 4 4	Vineland 104 Hayes-Binet 105 Vineland 115	4	Talks well; adjusts well to people; feeds himself and is toilet trained; explores his environment skillfully and purposefully; anticipated he will attend school for the blind that his brother attends; should do well; no vision

some hand tremor. Except for this case it seemed plausible to postulate that these blind children would continue to develop neurologically and mentally within a normal range throughout childhood. Even the child with the double handicap of blindness and deafness performed so well and in so many ways on developmental testing, it was felt that he, too, might continue to show evidence of normal mentality throughout childhood.

A four-year follow-up study of these blind children will be the subject of this article.

Material and Method

The original control group of premature infants with vision who were tested in the first year of life with the Gesell test were retested between the ages of 3 and 6 years, using the Vineland Social Maturity Scale and the Stanford-Binet Form L test. This testing was done by one of the examiners who had not seen them previously (C. F. or R. W.). Three children were not available for retesting. These children were originally tested as part of a routine program in an adoption agency before final adoption was accomplished. The follow-up testing was a voluntary courtesy of the adopting parents.

The 10 premature infants with blindness as a result of retrolental fibroplasia were originally referred for testing by the Field Service for Blind Preschool Children of the California School for the Blind. These children are all under various private and clinic medical care. Thus, the follow-up studies have only been through the close relationship of the families of these children with the staff of the Field Service for Blind Preschool Children, and the willingness of these families to return for follow-up interviews, and not through a medical care program. There is, therefore, some lack of detail with regard to medical problems and physical development.

All of the children were seen between the ages of 18 months and 3 years of age by the original tester (A. H. P.). At this time they were seen in a play situation for observation, and the parents were interviewed. A general evaluation of their progress was made on this basis. Although some attempt was made to use the Gesell test, it was found to be unsatisfactory in the hands of this tester in this age period with blind children.

Nine of the children were seen again for general observation and testing between the ages of 3 years and 5 years. The parents were also interviewed. The Vineland Social Maturity Scale and the Interim Hayes-Binet Test for the Blind[17] were used when applicable for this evaluation. This testing was done by the two examiners (C. F. and R. W.) who had not seen the children previously and did not know the results of the Gesell tests done in the first year of life or of the second play observation evaluation. One Child, Case 7, had moved to another city and was not available for testing and interviews after 18 months of age. However, through the courtesy of her parents and interested professional workers* in her new community, testing and observation evaluations were made available to us.

Electroencephalograms were done on six of the blind children at ages 3 to 5 years. One child (Case 10) was awake and not sedated. The others were sedated with chloral hydrate so that sleep tracings could be obtained. An electroencephalogram attemped on Case 2 was unsuccessful, owing to extreme hyperactivity even under heavy sedation with chloral hydrate.

Finally, biographical material was obtained on each child. This was obtained from the records of the workers of the Field Service for Blind Preschool Children, from our various interviews with the parents, and other agency, hospital, or medical records made available to us.

Developmental quotients or intelligence test scores of more than 80 were considered normal, recognizing 80-90 scores as dull normal according to definition.[18] Scores of less than 80 were accepted as indicating mental retardation but not necessarily mental deficiency. Mental retardation as used in this paper indicates less than normal functioning on any basis, whether through emotional interference, environmental deprivation, or inadequate mental potential.

A child is generally considered blind if the vision in his best eye corrected is less than 20/200. However, vision considerably less than this can be useful in moving about and in exploring new objects and places. Though all of the blind children were considered to have no vision when first seen, several developed useful vision of some degree. When this has occurred, this is indicated as useful vision. Those children with only vague regard for bright light were classified as having no vision.

Results

The results of the retesting of the control group of prematurely born infants with normal vision revealed none of the seven tested as mentally retarded (Table 1), assuming only scores below 80 as indication of mental retardation, except Case 2, and this

* Miss Miriam Norris, Director, Greater Chicago Project on Blind Children.

child had a normal score on the Vineland Social Maturity score.

The retesting and clinical evaluation of the 10 prematurely born children with blindness as a result of retrolental fibroplasia revealed 6 children who could be considered as functioning within the normal range (IQ 80 or above) and 3 functioning at a mentally retarded level (IQ below 80) (Table 2). One child, Case 8, could not be adequately tested because of his combined hearing and vision defects. Five different observers have seen him in play situations and believe he has normal mental potential. This is based on the amount of his investigative activity and the creative variation in his spontaneous play activities.

The three blind children who were found to be functioning at a mentally retarded level are Cases 1, 2, and 3. All three of these cases, however, have been considered by several observers to have normal mental potential that has been functionally suppressed because of severe emotional problems. The details of these problems and the conclusions of the observers are included in the biographies. It is of interest to note that these three children had the lowest birth weights (Table 2). Their gestational ages as reported, on the other hand, are similar to those of Cases 5 and 7, who are doing well. It is also noteworthy that all three are recorded as having no vision, in contrast to Cases 4, 6, and 9, who have a little vision and are doing well. But it should also be pointed out that Cases 5, 7, and 10 also have no vision and are doing well.

Some of the physical characteristics of the 10 blind children that might have a bearing on their mental and social development were recorded (Table 3). Electroencephalograms were done on six of the children. Two of these were read as mildly abnormal. In both instances this

TABLE 3.—*Some Physical Characteristics of Ten Prematurely Born Children with Blindness as the Result of Retrolental Fibroplasia*

Case No.	Birth Wt.	Present Age (April, 1958)	Head Circ. (Present)	Neurological Signs	Electroencephalograms * at Present Age	Vision at Present
1	2 lb.	4 yr.	48 cm.	None	Mildly abnormal EEG because of increased prominence of slowing during light sleep — more than expected for age	None
2	2 lb. 3 oz.	4 yr. 4 mo.	49.5 cm.	None	Unsuccessful attempt due to activity of child even when heavily sedated	None
3	2 lb. 3 oz.	5 yr. 2 mo.		None	Normal	None
4	2 lb. 7 oz.	4 yr. 5 mo.	45 cm.	None	Normal	Right eye — none Left eye — useful vision
5	2 lb. 10 oz.	4 yr. 8 mo.		None		None
6	2 lb. 12 oz.	4 yr. 5 mo.	50 cm.	None	Mildly abnormal EEG with moderate to high potential slow 1-3 cps waves over the posterior scalp areas; more slow 1-3 cps activity than expected for her age	Right eye — 0 Left eye — useful vision
7	2 lb. 12 oz.	5 yr. 10 mo.				None
8	3 lb. 3 oz.	4 yr. 6 mo.	50 cm.	Deafness bilaterally; slight increase in knee jerks bilaterally	Normal	Left eye — none Right eye — useful vision
9	3 lb. 6 oz.	6 yr. 3 mo.	48 cm.	None		Left eye } useful vision Right eye } With correction using both eyes 10/70
10	3 lb. 8 oz.	4 yr.	48.5 cm.	None	Normal	None

* All electroencephalograms were interpreted by R. W. Walter, M. D., of the Department of Neurology, School of Medicine, University of California at Los Angeles.

consisted of more 1-3 cps waves being present than was considered consistent with the age of the child. It was felt that not much emphasis could be put on these findings, because of the minimal nature of the deviation from normal. One child with these EEG findings, Case 1, was in the group functioning at a retarded level and having emotional problems. The other child with abnormal EEG findings seems to be doing well mentally and socially. Furthermore, two of the children functioning at a retarded level and having emotional problems had normal EEG's.

The only child with neurological findings was Case 8. This is the child with bilateral deafness. He was considered to be somewhat ataxic when seen in the first year of life. When examined at 4 years and 6 months of age, he was walking well and with a normal gait. However, both knee jerks seemed to be hyperactive. He walked without support by 22 months of age, which is comparable to the other children.

Though several of the children had rather small heads (Table 3), there was no apparent correlation of head size with mental or social performance (Table 2).

All of the children were considered to have no vision when they were first seen. During the follow-up period three of the children, Cases 4, 6, and 8, developed useful vision in one eye of a very limited nature. They are still regarded legally as blind. One child, Case 9, developed sufficient vision to be able to read large print with glasses. She would not be considered legally blind. Several of the remaining children would look vaguely in the direction of a bright light. This was not considered useful, and these children were classified as having no vision (Table 3).

The age of successful development by the blind children of four self-help tasks was determined (Table 4). These tasks were (1) walking without support; (2) feeding self with a spoon; (3) talking in sentences; (4) toilet training (indicating toilet needs). The three children (Cases 1, 2, 3) considered to be functioning at a mentally retarded level were not doing any of the items except walking without support when they were last seen at 4 years of age or older. One child, Case 3, did talk some in sentences at 2 years of age and then stopped talking. Two of these children were no

TABLE 4.—*The Age of Successful Development of Four Self-Help Tasks by the Ten Prematurely Born Children Blind as the Result of Retrolental Fibroplasia*

Case No.	Present Age in Months (April, 1958)	Walking Without Support	Feeding Self With a Spoon	Talking in Sentences	Toilet Trained	Vision at Present
1	48	32 mo.	0	0 (Says a few words)	0	0 *
2	52	24 mo.	0	0 (Says a few words)	0	0
3	63	14 mo.	0	24 mo. (Has stopped talking at present)	0	0
4	53	27 mo.	30 mo.	30 mo.	36 mo.	Right eye — 0 Left eye — useful vision †
5	56	18 mo.	36 mo.	24 mo.	28 mo.	0
6	53	15 mo.	24 mo.	24 mo.	24 mo.	Right eye — 0 Left eye — useful vision
7	70	14 mo.	30 mo.	24 mo.	20 mo.	0
8	54	22 mo.	48 mo.	0 (deaf)	48 mo.	Left eye — 0 Right eye — useful vision
9	75	18 mo.	48 mo.	18 mo.	36 mo.	Left eye } With correction using Right eye } both eyes 10/70
10	48	20 mo.	36 mo.	30 mo.	48 mo.	0

* Some of the children indicated as having no vision appeared to look vaguely at bright lights. This seemed to be of no value to them in getting about.

† Useful vision indicates ability to distinguish an object held near the eye but vision not measurable by the usual standards.

slower in walking without support than several of the other children who ultimately did well. It would appear that the tasks more related to social-cultural factors were the most adversely affected.

The average age for the successful accomplishment of the task of walking without support was 20.4 months for the entire group. The average for the three retarded children was 23.3 months. The three mentally normal children with no vision walked at an average age of 17.3 months. The mentally normal children with vision excluding the deaf boy, Case 8, walked at an average age of 21.3 months. It would appear that the small amount of vision did not significantly aid them in learning to walk. In fact, with respect to all of the other tasks the three mentally normal children with some vision and the three without had essentially equivalent average ages of success.

The deaf-blind boy learned to walk without support almost as early as the rest, but the other tasks were delayed, though no more than the maximum time for others in the group. He has not learned to talk but this is in progress, and it is anticipated that he can be taught to talk. It would seem that he does hear some sounds, especially with his hearing aid, but adequate testing has not been possible as yet. This small amount of hearing undoubtedly helps him, as does the small amount of vision in his right eye. Nevertheless, it is very difficult to communicate with him. His progress to date is a great tribute to his parents.

Tabulation of various characteristics of these children does not adequately describe their development, though it does aid in emphasizing various aspects of development for comparative purposes. The biographical summaries of the development of all 10 of the blind children are included to give a more complete picture of their development. This also permits a more critical evaluation by others of some of our conclusions.

Comments

The greatest evil that can befall a blind child is to be judged mentally retarded early in life and thereby be deprived of any opportunities for intellectual development. Almost as serious for both the blind child and his parents is the failure to recognize a child with serious mental impairment early enough to spare both the torment of trying to achieve impossible goals.

It has been our experience from this study, and requests to examine other blind children that have come incident to this study, that the most difficult age period in which to evaluate a blind child is after 1 year of age and before language is well developed at approximately 3 years. As indicated in Table 4, common cultural-social items are delayed in development, even in children who later prove to be mentally normal on intelligence tests. These items were even further delayed in the severely emotionally disturbed children. Furthermore, in these latter children, language is very delayed in developing, thus eliminating this avenue of intelligence testing. The outcome of the three cases we have judged to have normal mental potential that is not manifest because of their emotional disturbances is, of course, still in doubt.

Some of the other children gave outside observers and sometimes their parents cause for concern regarding their development, between the ages of 18 months and 2½ years. In these instances, as with all of the children, biographical information of their activities at home, relationship with their siblings and parents, and general play activities, were often more helpful than any tests.

Our observations on the social development of these children were similar to the findings of Maxfield.[18] On the basis of her experience with blind children, she has developed the Maxfield-Bucholz Social Maturity Scale for blind preschool children. We chose to use the Vineland Social Maturity Scale because of our greater familiarity with it. In the use of this scale there was some revision of the scoring to

allow for the blindness. We found this a very useful evaluating tool.

After some experience with blind infants and preschool children, the quality of their play and interest in their surroundings impresses one as an important method of evaluation. The imagination exhibited in inventing ways of exploring new objects is impressively suggestive of good mental functioning. This is noted repeatedly in the biographical notes of the workers of the Field Service for the Preschool Blind.

The original study of these 10 blind children demonstrated that the Gesell Test is applicable to blind prematurely born infants in the first year of life.[11] All of the infants scored within the normal range. On subsequent follow-up, six of these children are definitely mentally normal. The deaf-blind boy is performing well for a child with such a double handicap, but one cannot be certain of his mental development. The remaining three children are functioning at a mentally retarded level. However, their poor level of functioning would appear to be on the basis of emotional problems. Two, Cases 1 and 2, have begun to improve some since the acceptance of psychiatric help by the parents. The parents of the third child have not accepted any psychiatric help.

From these observations and the previous comments regarding the difficulty of evaluating blind infants in the toddler period, it would appear that development testing of blind infants in the first year of life is a significant adjunct to any evaluation program. It has been of considerable help to the parents, doctors, and field workers to have this early evaluation as a source of encouragement in working with the children. Otherwise it was not until the children had good language development that they had any generally accepted evidence that the children were normal mentally. It is interesting to note that Nelson and Richards[19,20] found a better correlation between infant testing at 6 months and mental test scores at 3 years than between 12 months and 3 years. These were normal children with vision. They related this to the infant test structure.

In reviewing the biographies of these children, one finds that the role of the family in aiding these children achieve their full potential for development is impressive. In early infancy this seemed to be a matter of giving the infant the security of acceptance and a wide range of sensory and emotional experiences. In the toddler period, the children needed a feeling of confidence in themselves to move on to independent action and self-help. Some of the families seemed to be able to aid them in this more than others. Often the field workers could help some by encouraging the parent in allowing the children more independence and by giving the parent confidence in the child's abilities. Then the children needed an expanded social experience with children their own age and adults outside the home to ready them for schooling. This is a trying time for the parents, who are concerned about the attitudes of other adults toward their blind child. They are also afraid that the child will not be able to play successfully with other children.

The fear of the attitudes of other adults was often justified. The blind children were not accepted in some nursery schools or play groups by the adult directors. One child guidance clinic refused to accept a case because the child was blind. However, other children accepted the blind children well. Sighted children will readily include a blind child in their play, especially in the nursery school age period.

Only two of the children are in elementary school and both are in schools with sighted children. One of these children sees enough to read the large print of primers but the other is totally blind. She attends a special Braille program in the school. So far she is doing well. It will be interesting to follow the rest of the children as they go through elementary school.

The development of these blind children in the preschool age period has been a pleasure to observe and surprising in its normal progression for most of the children,

despite their additional handicap of premature birth.

Biographies of the Ten Prematurely Born Children Blind as a Result of Retrolental Fibroplasia

CASE 1.—This boy was born March 19, 1954, of Japanese parents 12 weeks prematurely. The pregnancy and delivery were uncomplicated. His birth weight was 2 lb. (905 gm.). Retrolental fibroplasia was diagnosed at 3 months of age. The retina of the right eye was described as totally detached and that of the left eye as incompletely detached. He has no vision at the present time, though at times he may look toward a bright light.

The parents have found it exceedingly difficult to accept this child's blindness. One relative reprimanded the doctor severely for saving the child's life. The parents still have not informed the maternal grandmother of his blindness and she has not seen him. A brother, 4½ years older, has the closest relationship in the family to this boy. There are no other children in the family.

First year (0-1).—During this year there was continual searching on the part of the parents for a cure for his blindness. He was kept in his crib most of the time, overly dressed and often surrounded by pillows. Toward the end of the year, after much encouragement by the field worker, the child was allowed on the floor to play and was given more freedom.

He was first tested at 27 weeks of age, when he performed at an estimated 15-week level, which was compatible with his age corrected for 12 weeks of prematurity. He did best in the prone position, rocking on his stomach with arms and legs extended. When nursing he would pat his bottle. These are 20-week items. He held the ring indefinitely and had a spontaneous social smile and chuckled. His social responsiveness was considered surprisingly good.

However, during the remainder of the first year his development was slow. By the end of the year he was just able to sit alone. He continued to seem happy and to be socially very responsive, especially to his brother.

Second Year (1-2).—His mother seemed unwilling to let him develop independent action when he was ready for it. At 16 months he was still on puréed foods and would not touch any food or hold his bottle. At 17 months he stood holding onto furniture and said "ma-ma." By 2 years he walked freely around the house holding onto furniture, but his exploration of toys was limited to banging and he seemed apprehensive in new situations.

Third Year(2-3).—He was seen for a play evaluation at 25 months, at which time it was noted that his exploration of toys was extremely limited. He would either bang them on the floor or flick them with his finger. He did explore the room by walking, holding onto furniture, and played a game of running around his mother, clutching her skirt. Despite this seeming social relationship with her, it seemed difficult for her or the examiner to break into his repetitive activity.

At 29 months of age the entire family went on a two-week auto trip and following this almost all motor activity ceased, except for flipping objects with his hands or tapping his teeth. He seemed to shut off all relationship with people, and his mother's voice elicited no response. By 32 months he was responding again. He could walk without assistance and seemed happier. He permitted more personal contact and would say a few words, such as "okay, car, cookie." However, shortly after this he developed a severe sleep problem. He would awaken at 1:00 a. m. and cry and scream until 3:00 a. m. This lasted several months. Sedation did not help. The sleeping problem was somewhat improved by 3 years.

A Vineland Social Maturity Test given at this time was scored as 54. Though no direct psychological testing could be done at this time, his behavior suggested to the psychologist severe emotional disturbances as a predominant factor in his poor functioning.

Third Year (3-4).—The mother became increasingly concerned about his withdrawn behavior and his slow development. She wanted help, and an effort was made to get the boy into a child guidance clinic and nursery school. They rejected the case because of the blindness. The field worker went to the home frequently and he developed a close relationship with her. The mother perceived this and was able to talk about her own difficulty in establishing a relationship with the boy. Finally, some help in child guidance was obtained for the mother, and an arrangement was made for an experienced nursery school teacher to spend one hour a day with him at his home. Progress has been slow, but he seems more responsive to people and especially to his mother. He sleeps well, his vocabulary is increasing and he tolerates being placed on the toilet. He still refuses to feed himself.

The question, of course, remains whether this boy is primarily emotionally disturbed and, therefore, functioning at a retarded level or whether he is primarily mentally retarded owing to organic brain damage. An electroencephalogram was done at 4 years of age and was read as a mildly abnormal EEG because of the increased prominence of slowing during light sleep over that one would expect for patients of his chronological age. This was considered a minor deviation. His good early development, especially in the social area, has been assumed to be a sign of possible normal potential in this case. He seemed to regress in his

second year. It is hoped that with psychiatric help for the child and family, he may achieve a near normal development.

CASE 2.—This boy was born on Nov. 27, 1953, 12 weeks prematurely. His birth was 2 lb. 3 oz. (990 gm.). His mother had had three miscarriages and one premature infant of six months' gestation who died at birth. She stayed in bed throughout her pregnancy with this boy. He was discovered to have retrolental fibroplasia before he left the hospital at 2½ months of age. He was considered then to be completely blind. He may see bright light now, although this is questionable. His general health has been good. There have been no other children.

At first the parents said they were so happy to have a live baby that they did not care if he was blind. The father was almost aggressively defensive and was unable to be critical of anything the boy did or of his reactions to the boy. His expressed motivation was to make the boy happy, and to do this he tried to entertain and amuse the child. He was unable to modify this as the child grew older and attempted to become independent. The mother was disappointed in having a blind child, but could not express or recognize this because of her husband's attitude. She became very fearful about the boy's health and safety. She was afraid to have him move about, thinking he would injure himself.

First Year (0-1).—This boy was first seen for Gesell testing at 39 weeks and 3 days of age. His best performance was standing at the rail of the crib when placed there and bringing the cube against the cup in the table top situation. These are 36-week items. At a 32-week level, he did all of the items except sit without support. He was given a developmental level of 31 weeks, which was 4 weeks in advance of his corrected age of 27 weeks. He, therefore, was given a developmental quotient of 115.

At 10 months he could sit well without support, but was kept confined to a folded sheet on the rug because the mother feared the dog hairs on the rug might be injurious to him in some way. By 12 months he was moving about in a walker and would drink from a glass. He was not allowed to touch food because this caused a mess.

Second Year (1-2).—At 15 months the mother felt he could not stand except when holding onto her. The field worker helped her to accept letting him stand holding onto furniture and other objects. At 19 months he wanted to walk everywhere holding his mother's hand. This occupied most of her day. He could creep very fast, but the mother feared he would bump his head. He was allowed to finger feed himself some table foods.

At 22 months he was beginning to respond to toilet training. He walked well, holding on and took occasional steps alone. He did not talk. His mother dressed him on the bathinette and kept him in a play pen most of the time. He was becoming irritable and demanding. He refused the bottle and also milk from a cup.

By 24 months he was described as irritable, resistant, showing little personal relationships with outsiders except an aunt. He was a severe sleep problem. His father walked with him every night to put him to sleep. He rubbed his eyes a great deal. He could walk alone and climb a ladder to his slide and invented a game of rolling a ball up the slide and then catching it on the way down. His mother said she felt closer to him. He was increasingly demanding of his father and screamed to be held. The father was beginning to resent his demands.

The parents state that he was beginning to talk, feed himself, and to be toilet trained at about 2 years of age. Then they started to put calsulfhydryl drops in his eyes. These were so painful to him that they only continued them for two weeks. However, the father felt that he regressed behaviorly during this time. After the drops were discontinued they continued to give him sulfhydryl powder in his food for six months. There was no improvement in his vision.

Third Year (2-3).—He was seen at 26 months for a play evaluation. His walking and his exploration of the room and of the toys was very impressive. His greatest lack was in the language area. He was reported to say a few words, but no combinations of words. In the interview his mother described his fear of the toilet and resistance to toilet training, his inability to go to sleep at night, and his unwillingness to hold a cup or spoon. The conflict between the mother and child on all problems of socialization seemed to be overwhelming the mother. She was obviously indecisive in all her actions. At that time he was considered to show some evidence of normal mental potential, but significant emotional disturbances.

During the remainder of the year this boy made little progress. His language did not improve; his sleep problem persisted, and he became more aggressive towards his mother. His father became more punitive as he was unable to keep up with the boy's demands. Psychiatric help was advised and offered in various forms repeatedly and was not accepted.

He was seen at 38 months for psychological testing. He was hyperactive, perseverative, and highly distractable. He was able to perform the nonverbal items of the Hayes-Binet test at a 36-month level. This was not considered a valid test, but an estimated score of 105 was given. On the Vineland Social Maturity Test he was given a score of 73. The father was observed to be

very anxious, overprotective and oversolicitous. He attempted to anticipate and gratify all of the boy's needs. The tester (R. W.) felt that there was suggestive evidence of organic brain damage compounded by difficulties in the parent-child relationship.

Fourth Year (3-4).—During this year the parents made a greater effort to evaluate their feelings toward their son and to be more critical of their management of him. They found more activities for him outside the home. He enjoyed going in the neighbor's swimming pool, although he did not respond to other children in the pool. He was accepted in a small church nursery school. The teacher accepted him well, and he tolerated the other children but did not participate in their activities. His hyperactivity, aggressiveness, and negativism were major problems for the teacher.

Toward the end of the year the father began to do all of his work at home. This put more pressure on the child and the mother. The sleeping problem was aggravated. However, the boy began to babble some with his mother and occasionally would go to the toilet independently.

At 46 months of age he was seen for psychological testing by R. W. a second time. He was less hyperactive and distractable and showed improvement in his ability to relate to others. His over-all behavior evidenced a decidedly higher level of integration. Nevertheless it was still not possible to do valid intelligence testing. His language development was still very poor, but his comprehension was very good. Though on a Vineland Social Maturity Scale he scored 50, it still seemed likely that his mental potential might be normal.

Present Evaluation.—He is now 4 years and 4 months of age. He is very hyperactive and limited in his ability to relate to people. He does not talk in sentences, but says words. He will feed himself with his fingers some and will sometimes go to the toilet. He will sleep through the night only if he is with his father. The family has sought help from a child guidance clinic. This clinic has recommended psychiatric care for this boy outside of his home and guidance for the parents while he is away. This has been arranged. An electroencephalogram attempted at this time was unsuccessful because of inability to sedate him adequately even with large doses of chloral hydrate.

The general opinion is that this boy is primarily emotionally disturbed. If the proper kind of help is given, it is felt that this boy can achieve a reasonably normal level of mental and social functioning.

CASE 3.—This girl was born Feb. 2, 1953, 10 weeks prematurely. Her birth weight was 2 lb. 3 oz. (990 gm.). The pregnancy was uncomplicated until hemorrhage initiated premature labor and delivery. The presentation was vertex and no anesthetic was required during the delivery. The baby did not cry immediately, presumably because of mucus obstruction in the trachea. Respirations were established with difficulty. She was diagnosed as blind, as a result of retrolental fibroplasia, by 3 months of age. Her blindness has been complete to the present, though she may perceive bright light. Between 7 months and 3 years of age she had recurrent glaucoma with ocular tension up to 84. At first this was controlled medically, but ultimately surgical treatment of the glaucoma was necessary. This was followed by some iridocyclitis. At one time removal of both eyes was recommended because of apparent persistent pain despite reduced intraocular tension. There was conflicting medical opinion relative to this and this was never done.

Her parents had wanted a child for a long time and this girl was their first born. At first they seemed to be very close to her and enjoyed her very much. However, their feelings about her blindness were very deep and they were very concerned about what other people thought of her. They found it difficult to talk about her blindness to others. Gradually the mother's relationship to this child seemed to be that of a distant observer. There were many pats and kisses but she was tense in expressing real affection. She often talked baby talk to this child in a high, unnatural voice. She became well informed on medical terminology and on blindness and continually searched for opinions from many doctors but was unable to accept any of these opinions.

The marriage became an unhappy one with several separations. Another child, a beautiful normal girl, was born when the first girl was 13 months of age. The relationship between the two girls is not a close one.

First Year (0-1).—In the first few months of life the child cried a great deal, had diarrhea and vomited. Goat's milk was said to have cured the diarrhea. By 5 months of age she was a happy baby, responsive and smiling. At 7 months of age she stood and bounced when held supported, held toys, played with her own hands, and laughed aloud. By 11 months of age she could pull herself to a standing position, cruise along the rail of her crib, feed herself with her fingers, jabber and imitate sounds, and drink from a cup. She was described as a merry, active youngster. There were, however, two major problems. She had a bizarre sleep routine, preferring to be awake until well after midnight and to sleep most of the day. The parents either could not or did not try to change this. She was also noted to have some swelling of the eyes, and glaucoma was diagnosed. Though tensions as high as 48 mm. were measured, she showed little evidence of pain and medical management seemed to be satisfactory.

Second Year (1-2).—A developmental test was done at 53 weeks of age. She sat well without support and could pivot in the seated position. She pulled herself to a stand at the rail of the crib and cruised along it. She could walk with only one hand held. She used her index finger well in exploring items and poked at the clapper of the bell to explore the source of the sound, and removed the round block from the form board. She said "ma-ma" and "da-da" and could wave "bye-bye" and "pat-a-cake." She drank well from a cup. She was given a developmental level of 44 weeks, which was considered compatible with her corrected age of 43 weeks. Her developmental quotient was 102. At that time the comment was made that both parents enjoyed playing with her and seemed to give her adequate affection and stimulation.

Shortly after this testing the intraocular tension increased in both eyes, and surgical correction was necessary. Following this she became fretful and seemed to have more pain, even though the intraocular tensions were normal. It was thought that she might be suffering from iridocyclitis. None of the treatments seemed to relieve the distress. She slept poorly even with sedation, and her appetite diminished and she became easily fatigued. Her weight was only 17 lb. (7,710 gm.). This period was described as "veritable hell" for the entire family. Her sister was born about one month before the eye surgery.

At 18 months of age she was still eating poorly and was fretful a great deal of the time. By 21 months she was happier and more friendly and her sleeping problem was less severe. Her vocabulary was large and she talked in phrases and short sentences, answered questions and enjoyed saying difficult words. She was very active. She enjoyed her swing and went in and out of the house into the yard alone. She was eating better.

Unfortunately, right after this the mother had to leave the family a few days and return to her home town to take care of her father. Then the entire family returned to her father's home to settle family affairs. This child did fairly well in this strange place but became very touchy and sensitive.

Third Year (2-3).—After the family's return from this trip she seemed to regress. She remained active and eager in her manipulation of toys but she preferred solitary play. She did not relate to people other than her parents. She chattered to herself in clear speech but would not talk to others. Briefly, she was enrolled in a cooperative nursery school. She did not relate to the other children but would accept close contact from the teacher. By the end of the year the parents felt she had regressed both physically and mentally. They attributed this primarily to eye pain. It was found that there was an increase in the tension in the left eye. Enucleation of both eyes was recommended by one ophthalmologist but not by another. The parents were undecided. At this time her speech was still clear and she had a large vocabulary but talked mainly to herself. She rode a tricycle and would climb up the steps of a slide.

Fourth Year (3-4).—At the beginning of this year she had pneumonia and was very ill. After this the parents stated that she seemed to have cramps in her legs and intestinal distress. Generally she was unhappy and slept poorly. She would cry continuously for long periods of time and could not be consoled. She would stay in her own room. Her speech was hardly understandable. She climbed on her parents and on other people as if they were furniture. Various sedatives and tranquilizers were only of temporary help.

At 38 months she was seen for play evaluation. She showed considerable interest in various toys for brief periods but her exploration of these toys was limited. She talked to herself in a jargon of her own. Occasionally she would say intelligible words, but these were generally not directed at anybody in the room. In general she ignored the people around her. She seemed to hear what was said but gave no recognition of this. The impression was that her mental potential might be reasonably good, but that she was becoming progressively withdrawn. At that time she weighed 23 lb., was 37 inches tall, and had a head circumference of 46.5 cm.

The parents were very concerned about her physical development and her unexplained periods of distress. For this reason she was hospitalized at 42 months of age for observation and laboratory studies. Laboratory tests revealed the following: fasting blood sugar 97 mg.; phosphorus 5.1 mg.; calcium 5.3 mEq.; B. U. N. 11.5 mg.; hemoglobin 11.7 gm.; x-ray studies of the skull, upper and lower gastrointestinal tract and an I. V. pyelogram were all normal; wrist x-rays for bone age were estimated as a carpal age of 38 months; an electroencephalogram was normal. She had no attacks of distress while in the hospital. A psychiatric consultant felt that her regression was primarily on an emotional basis. Psychiatric help was recommended at that time but the parents did not wish to accept this kind of help.

Briefly she seemed to improve somewhat after her hospital stay. She began to repeat nursery rhymes previously known but otherwise had no speech. By 48 months she had become more aggressive and would bite herself and her parents. In play with toys she mouthed everything. Her motor activity involved mainly rhythmic and circular body movements. Her emotional responses were inappropriate. Her greatest response was to

"rough house play," which brought on gales of laughter.

Fifth Year (4-5).—Early in this year the parents attended some psychiatric group meetings for a few weeks. During this time the girl improved some in that her perseverative circular body motion could be interrupted and her activity could be redirected. She appeared more relaxed. Her play with toys was more meaningful. She seemed more aware of her environment.

At 55 months of age she was seen for psychological testing. It was not possible to do intellectual testing in an objective manner at that time, because she was too withdrawn. She did perform a few items on the Hayes-Binet test at a 42-month level. The tester's general impression was that the depth of emotional distrubance in the child was sufficient to account for the behavior retardation. During the remainder of the year she seemed to make no progress. The parents became very hostile to the idea of psychiatric help. One doctor informed them the child was severely brain damaged, and placement in the state institution for the mentally retarded was considered by the parents. A second electroencephalogram was normal. Another doctor consulted advised psychiatric help. When last heard from the child was 64 months of age, and the parents were taking her to still another diagnostic clinic and were dissatisfied with it.

This child developed so well in the first two years of life it seems likely that she had and probably still has a reasonably normal intellectual potential. It would seem that her retarded functioning at the present time is primarily due to severe emotional problems. To date every effort to get this family to accept psychiatric help has been unsuccessful except for one brief period. It is still possible that this kind of help may be accepted and that this child might be returned to a reasonably normal intellectual and social functioning level.

CASE 4.—This girl was born Oct. 27, 1953, reportedly only 8 weeks prematurely. Her birth weight was 2 lb. and 7 oz. (1,105 gm.). The pregnancy had been complicated by several threatened miscarriages with spotting. The baby was delivered by cesarean section because of bleeding, presumably due to placenta previa. Retrolental fibroplasia was diagnosed while she was still in the hospital. She was thought to be completely blind in early infancy, but at present seems to have some peripheral vision in her left eye and may be able to distinguish some large objects. She certainly sees light.

There are three older children in the family, who were ages 18, 16, and 11 at that time. The family has always been in a poor financial state. They have lived in low-cost furnished apartments with no major effort made to improve the shabbiness of these apartments. On the other hand, the family has been cohesive. The older children have assumed financial responsibilities for themselves and sometimes for the entire family. The older daughter is now self-supporting and attending a university. They all shared in the care of this baby and had good relationships with her. She was always included in family camping trips, picnics, and other activities.

First Year (0-1).—This girl was an easy baby to take care of, according to her mother. At 6 months she sat with support and would hold toys; by 7 months she stood with hands held, and at 8 months would sit momentarily alone and would "pat-a-cake." She was first seen for Gesell testing at 47 weeks of age, at which time she sat well without support; stood holding the crib rail when placed there; took the bell by the top of the handle, had a crude release of the cube; used her index finger to explore; and, said "ma-ma" and "da-da." She was very deliberate and slow, but thorough in her exploration and manipulation of each toy. Her mother described her as a quiet, thoughtful, happy child. At that time she localized all objects by sound and did not appear to use any vision. She was given a developmental score of 37 weeks on the basis of her over-all performance. Her corrected age was 39 weeks and this gave her a developmental quotient of 94. By one year of age she was reported to be eating all table foods, chewing well, and would feed herself a tuna fish sandwich.

Second Year (1-2).—She started the year by learning to handle a cup herself and to pull herself to a stand on furniture. By 18 months she could creep everywhere and could walk with two hands held, but did not like to do this. There was some concern about her left leg, because she tended to drag it (hip x-rays were negative). She enjoyed going with the family to the store. She was a very happy child.

At 2 years she seemed fretful and was eating poorly. She also had trouble going to sleep. Her mother thought her carious teeth were hurting her. She could stand momentarily alone, but not walk. She was toilet trained and her vocabulary was increasing rapidly.

Third Year (2-3).—She was seen for play evaluation at 25 months of age. She walked well and talked in short phrases and had an estimated 100-word vocabulary. Her general interest in people and social situations, as well as objects, was very good. She was considered to be developing normally mentally and socially. She had light perception in her right eye and possibly she could perceive gross objects. Her weight was 21½ lb. and height 33 in.

During the remainder of the year she became increasingly interested in and active in the world

around her. However, her appetite was described as poor, and she had difficulty in going to sleep at night. She liked to ride her tricycle. She was interested in being with other children and enjoyed chasing the family dog. She talked in long sentences. She began to assert herself at home, and her mother considered her at times a disciplinary problem.

She was seen at 34 months of age for psychological testing. She cooperated well and was given a score of 94 on the Hayes-Binet test and of 81 on the Vineland Social Maturity Test. The mild retardation in social progress was attributed to her blindness. Her over-all adjustment was considered good.

Fourth Year (3-4).—The feeding and sleeping problems gradually resolved during this year. She learned to play long periods of time by herself with blocks and dolls and other toys. She enjoyed long conversations and story books. She learned to climb stairs well. Briefly, she was in a nursery school where she adapted well. She could not stay because the family moved.

Present Evaluation (4 Years 5 Months).—She now takes care of all of her own needs, such as eating and toileting. She does not dress herself. She has good balance and can roller skate. She has excellent use of language and enjoys conversation. She enjoys being with children and adults and initiates her own play activities. An electroencephalogram done at this time was normal. She is considered normal mentally and socially. It is anticipated that she will enter a regular kindergarten and then go on to an integrated school with sighted children.

CASE 5.—This girl was born Aug. 8, 1953, 11 weeks prematurely. Her birth weight was 2 lb. and 10 oz. (1,190 gm.). The mother's pregnancy was reported as normal. She has one sibling, a brother 4 years older, who was born three weeks prematurely, but is perfectly normal. She was suspected of being blind at 4 months of age, but not definitely diagnosed as having retrolental fibroplasia until 6 months of age. She was considered to be totally blind at that time and she still is, although she may perceive bright light.

The parents considered her extremely fragile at first and expected very little from her. They were slow to give her adequate stimulation. However, the mother seemed to have great capacity to learn from her child and gradually stimulated her more and more. The relationship between the older brother and this girl was very good throughout. The total family relationship seemed strong and the mother received a great deal of support from her husband. The family have been financially well situated and both parents are intelligent people. Unfortunately, in the past few months the father has been critically ill.

First Year (0-1).—This girl was able to sit with little support by 8 months and could feed herself toast and cookies. At one year she was seen for Gesell testing. She could sit indefinitely without support. She stood at the crib rail and lifted her foot, but did not cruise. She did walk with both hands held. She drank from a cup and did sequential cube play. These were her best performances. She did essentially all of the items at 40 weeks except those requiring precise hand-vision coordination. She was given a developmental age of 43 weeks. Her corrected age was 42 weeks. Therefore, she had a developmental quotient of 100. Subjectively, she impressed one as better than the scoring would indicate because of her extreme interest and enthusiasm during her play.

Second Year (1-2).—Comprehension of language came in rapidly by 15 months and at 16 months she took a few steps alone and said "ma-ma" and "daddy." At 22 months she could run and name almost any object and sometimes used words to describe her activity. By 2 years she talked in sentences and played word games with her father. She did not like to be alone and followed her mother everywhere around the house. Sleeping was a problem. She cried at night and got in bed with her mother.

Third Year (2-3).—Socialization proceeded rapidly. Toilet training was complete by 28 months. She participated in household chores, such as setting the table, at this time. Play evaluation was at 29 months. Her play was extremely complex, including catching the ball when it bounced against her body and adapting to reversal of the form board with a few errors. Her conversation was expansive. She gave her full name and in response to the question "was she a boy or a girl" she answered correctly after some hesitation. Her language and comprehension seemed to be nearly at a 3-year level. There was no doubt in the observer's mind that she was functioning at or above a normal level mentally and socially. It should be added that her parents still found it necessary to feed her. However, by 3 she was feeding herself. During the remainder of the year her development continued rapidly. The sleep problem was resolved by steady firmness on the part of the parents. Her chief problem was fear of being away from her mother even for a few minutes.

Fourth Year (3-4).—She proceeded to gain more and more independence so that by the end of the year she could spend a day away from her mother without fear. She carried out complicated errands and enjoyed a visit to a nursery school. Plans were made for her to attend nursery school.

She was seen at 37 months of age for psychological testing. Her good language development and social adjustment made testing easy.

She was given the Wechsler Intelligence Scale for Children and achieved a score of 123. On the Vineland Social Maturity Scale she received a score of 122. There was no question about her advanced abilities despite her complete blindness.

Present Evaluation.—She entered a nursery school for half-day sessions and got along well without her mother. Attendance was irregular because of colds, and she was finally withdrawn because of her father's illness. The anxiety in the home about her father's illness brought on her fear of separation from her mother again. Aside from this problem, she does everything appropriate for her age and is alert and friendly and eager to learn. Her general health has been very good. It is anticipated that she will enter an integrated school program with sighted children and will do well.

CASE 6.—This girl was born Nov. 15, 1953, eight weeks prematurely, and weighed 2 lb. 12 oz. (1,245 gm.). The mother's pregnancy was normal except for some spotting at two months and premature rupture of the membranes two weeks before delivery. The labor was short, but normal. The mother was known to be Rh negative, but there were no problems with hemolysis in this child. The mother has had five subsequent pregnancies with only one living child and he required an exchange transfusion. He is 2½ years younger than this girl and is apparently normal.

Initially she was considered to be totally blind. The retina of the right eye is said to be completely detached, while that of the left is only partially detached. She now has useful vision in her left eye and can distinguish objects and colors. During her second year of life she had repeated respiratory infections and whooping cough and did not gain weight and at 18 months of age she was comatose for one day, said to have been owing to inhaled toxin from a plant spray mixture. She has been well since.

Her parents are intelligent and self-confident people who seem to have a strong relationship with each other. They mutually talked about their feelings about the blindness of their daughter and said that they came to terms with the problem early in her life. The mother said that at first it bothered her when other adults mentioned the blindness, but this does not trouble her so much now. She is now concerned with other children's comments to her daughter. The parents seemed to accept this child well and encouraged her independent activities at the same time, including her in all family activities. Her relationship with her younger brother has been good.

First Year (0-1).—This child immediately after birth was in an incubator for six weeks and received oxygen. She had been home for six weeks when retrolental fibroplasia was diagnosed. At that time she was returned to the hospital on the advice of her family physician and replaced in the incubator for another six weeks for gradual reduction of oxygen. She was in the incubator the second time from the age of 3 months to the age of 4½ months.

Developmentally she subsequently did well. At 6 months she sat momentarily without support and at 8 months pulled to a stand in her mother's lap. She was seen for Gesell testing at 41 weeks. She did essentially everything at a 32-week level except the pellet items. At the 36-week level she stood at the rail of the crib, had a radial-digital grasp of the cube, hit and pushed a cube with a cube, and hit the cup with the cube. She also imitated sound, responded to her name, and fed herself a cracker. On the basis of this testing she was given a developmental age of 34 weeks. Her corrected age was 33 weeks; therefore, she had a developmental quotient of 103. Although she later developed some useful vision, at that time it was noted that both eyes were deviated inward and she did not use vision at any time to locate an object, but felt for the toys with her hands. By a year of age she was walking all around the house holding onto furniture and the walls. The family noted that she appeared at times to make some visual responses.

Second Year (1-2).—She began to walk alone at 15 months and said several words. She had repeated respiratory infections and whooping cough, despite immunization. In the middle of this year on one morning she could not be aroused and she remained in a coma all that day. She was well the next day. It was thought that she had been poisoned by a toxic inhalant from some special spray mixtures at a neighbor's house. After this episode she continued to develop well. Her mother was very skillful in getting her to participate in the household activities. She was feeding herself well by 2 years and talked in sentences. She was also toilet trained. Her vision was definitely useful and she obviously explored objects by holding them close to her left eye.

Third Year (2-3).—In this year she began to use her limited vision more and more and seemed to operate much like a seeing child. When seen for play evaluation at 2½ years of age she played, talked, and socially behaved like a 2½- to 3-year-old child. Her relationship with her parents was exceptionally good. She had enough vision in her left eye to identify objects in pictures and name them.

She was seen at 33 months of age for psychological testing. On the Hayes-Binet test she received a score of 97 and on the Vineland Social Maturity Scale she was given a score of 120.

Fourth Year (3-4).—This girl continued to progress well. Her playmate was primarily her younger brother. She did not attend nursery school.

She did take dancing lessons, which she enjoyed very much.

An electroencephalogram was read as mildly abnormal with moderate high potential and random slow 1-3 cps waves over the posterior scalp area. This amount of slow 1-3 cps activity was described as somewhat in excess of what one would expect for a patient of 4 years.

Present Evaluation (4 years 5 months).—This child impresses everyone as a charming, confident, friendly, normal girl. She is to go to a regular kindergarten in the fall. She may later be in sight-saving classes and read large print. However, it is likely she will need to learn Braille also. Her general health is good now.

Case 7.—This girl was born June 13, 1952, thirteen weeks prematurely. Her birth weight was 2 lb. 15 oz. (1,330 gm.). The pregnancy and delivery were uncomplicated except for the prematurity. She was diagnosed as blind, as a result of retrolental fibroplasia, at 5 months of age. She had no vision in either eye then. At present she can see a little in a dark room, but nothing else. The parents were young, and wanted this baby very much. She was their first child. The parents were very upset when they first learned of her blindness, but very soon the wife and husband said "This is it and we've got to help her the best we know how." One of the mother's early statements to the field service worker was, "I'm afraid I'll be sorry for her and won't let her do enough." They were eager to help the child in every way possible, including not overprotecting her. They seemed to understand and accept suggestions from the field service worker very well. They appeared to be very successful in their management and understanding of this child until she was 2 years of age. After that they moved from the area and were not heard from again until the child became known to an agency for the blind in another metropolitan center. A follow-up report on this girl's present school progress was made available, and the mother wrote a lengthy follow-up report.

First Year (0-1).—This girl progressed very normally during her first year of life, and she was considered to be a happy baby. She was seen at 43 weeks of age for developmental testing. Her age corrected for 13 weeks of prematurity was 30 weeks. She sat steadily without support; stood with her hands held, and pivoted in the prone position. She had a radial digital grasp of the cube; held two cubes prolonged, and transferred objects from one hand to the other. She vocalized "da-da," imitated sounds; held her own bottle; and would feed herself a cracker. She was given a developmental age of 32 weeks and a developmental quotient of 106.

Second Year (1-2).—She was next seen at 18 months of age. Her corrected age was approximately 15½ months. She still seemed to be totally blind, although she objected to very bright lights. Both eyes had completely opaque retrolental masses. On physical examination she seemed to be perfectly normal otherwise, except that she was slender; weight 20 lb. 8 oz. (9,300 gm.); height 31½ in.; head circumference 18 in. She had been well, except for minor colds. On the play evaluation she seemed to be developing normally. She explored all of the toys fully. She played a game of rolling a ball back and forth between the examiner and herself. She enjoyed walking all around the room with both hands held. She was reported to walk up stairs with hands held and she would climb into a chair without help. She vocalized with a complicated jargon, said "mama" and "dada," and echoed words. Her favorite toys were a horn, a rattle, some blocks that rattled, a beach ball, and some keys. She did not like to hold anything soft or fuzzy like a teddy bear, or a soft doll. She would feed herself with her fingers.

She generally was a happy baby. She did have some sleep problems.

She was not seen again after this, since the family moved to another city. However, she was located in that city when she became known to an agency for the blind there. The report received from them was as follows: In the first grade she was in the regular classes part of the time, and in Braille classes the remainder of the time. At 5 years and 4 months of age she was given psychological tests. On the Hayes-Binet test she received a score of 131, and on the Maxfield-Bucholz social maturity test a score of 92.

Her mother reports enthusiastically of her progress in school. She can read three primers in Braille. She also has many outside activities. She rides a two-wheeled bicycle, roller skates, ice skates, and loves to go fishing. She also sings well, and takes singing lessons. Her mother states, "I can remember when I found out she was blind, the only thing I could think of was how empty and lonely her life would be. How wrong I was."

She is reported to be in good health, and at 5 years and 10 months of age weighs 56 lb. and is 46½ in. tall.

One would anticipate that she will continue to do well and have a full life.

Case 8.—This boy was born Oct. 6, 1953, 12 weeks prematurely. His birth weight was 3 lb. 3 oz. (1,445 gm.). This boy's mother has had seven pregnancies and has three live children. The first three pregnancies miscarried between the fourth and six months. The fourth pregnancy was carried to term, and this boy is 7 years of age and is healthy and normal. The fifth pregnancy was of six months' duration, and this premature infant died at birth. This boy, Case 8, was her sixth pregnancy. Her seventh pregnancy was of 30 weeks' gestation, and this girl is now one year of age and is normal and healthy. The mother received

estrogen and progesterone during all of the pregnancies. Her sister had two premature infants delivered after six months' gestation.

This boy (Case 8) was noted to be blind as a result of retrolental fibroplasia in the first five months of life. It was soon evident that although his blindness was complete in his left eye, he did have some vision in the right eye. At present he has useful vision in his right eye and examines all objects visually by holding them close to his eye. He guides himself visually when walking. His major problem is a severe hearing loss. Although he seems to hear a few sounds, he does not hear speech sounds, even with a hearing aid. He also has a minor orthopedic problem in that his left foot is 1½ sizes smaller than his right foot, and his left leg is about ¼ in. shorter than his right leg.

His parents are unusual people. This boy, with his combined difficulties of blindness and deafness has presented many problems. He has not been an easy child to handle, particularly in the first three years. These people seem to have a strong family unity, and when one parent gets discouraged, the other takes over. They seemed to complement each other. Both love and understand their boy. The father has felt the need to "teach" the boy while his mother has allowed him freedom in self-investigation. They have always been firm in handling him when this was necessary. The older brother plays well with him and is very considerate of him.

First Year (0-1).—When he was first taken home from the hospital at seven weeks of age, he slept all of the time and seldom cried. Then he became very restless when awake and tended to hold himself rigid, or thrash about and bang his head. He was first seen for a developmental examination at 47 weeks of age. His age corrected for 12 weeks of prematurity was 35 weeks. When placed in the seated position, he could sit without support prolongedly, if he leaned far forward. Otherwise he tended to stiffen his back and fall over backward. He stood holding onto the rail of the crib, and pivoted in the prone position. He could pick up small objects between his thumb and index finger in a scissors grasp, and had a radial digital grasp of the cube. He also released the cube intentionally and each time he released the cube he would go after another. He held his own bottle, and could feed himself a cracker. He transferred objects from one hand to the other with great skill, using his fingers nimbly. Of unusual interest during the examination was his lack of vocalization, and his exploration of several of the toys by banging them against his head. In the prone position he liked to bang his head. He was also not able to localize the sound of the bell to either side of his head. However, when he was prone with his head turned to one side, and the bell was rung close to his ear, he would stop banging his head and seemingly listen. From these observations, the parents were questioned in detail about his responses to sound, and it was mutually agreed that he probably had a significant hearing loss. This was the first time the parents had considered this possibility. Although his vocalizations were limited, he had squealed and laughed aloud.

The increased muscle tone in the legs and the tendency to arch backward was of concern to the examiner, as evidence of some neuromuscular disturbance. Despite his blindness, hearing loss, and increased muscular tension in his legs, his performance was generally very good, as detailed above. He was given a developmental age of 35 weeks and a developmental quotient of 100.

Second Year (1-2).—At 14 months of age he was seen at the John Tracy Clinic for the Deaf and was diagnosed as severely hard of hearing. The parents were also certain of his hearing loss by this time. Despite these handicaps at 15 months he was walking everywhere holding onto furniture, and also crawling on his hands and knees. He enjoyed people and was always smiling. However, he continued to pound his head and teeth with objects as a way of sensory exploration. He also slapped his ears until they were swollen. He made some sounds, mostly grunts and gurgles.

At 17 months he was seen at a special clinic for deaf children and given a hearing aid to wear in his right ear all day. Soon after this he was seen for a play evaluation. He had not been wearing the hearing aid long enough for the parents to evaluate its effectiveness. He did seem to enjoy wearing it and seemed to listen to it. However, he did not explore the sound of anything by bringing it close to the speaker. He was making sounds more frequently, but these were monotone vowel sounds. He still liked to tap objects against his head or teeth. When he was lying down, he rubbed his hands back and forth, or rubbed his back up and down, or bounced his body up and down. He seemed to use tactual and kinesthetic experiences to their fullest to explore his environment. This was so impressive that there was little doubt that he had normal intellectual potential. There was no longer any concern about a neuromuscular disorder. The reflexes were normal, and no increased muscle tone was evident. He weighed 24 lb. 7½ oz. (9,395 gm.) and was 30 in. tall. His head circumference was 45 cm.

At 22 months he began walking without support. He jabbered and made noises when listening to music. He finger-fed himself and would eat table foods. He was seen for another play evaluation at 23 months of age. He sat very steadily and would lean far forward and touch his head to the floor. He preferred to be standing, or on his hands and knees. He localized the toys immediately visually

with his right eye. He even located and picked up a small red pellet. When he was holding a new object he tended to bring it close to his right eye for careful inspection. He did not vocalize as much when he was not wearing his hearing aid. When he was wearing it he made a great deal of noise, but mostly a wailing, siren-like sound. When the hearing aid was in his right ear, he gently poked his left ear. He was very impressive in his play, body movements, vocalizing, manipulation of objects, and interest in his environment.

Once a week he received auditory training at the clinic for deaf children.

Third Year (2-3).—Early in this year he was given a separate hearing aid for each ear. This seemed to help him localize sounds in space. There was some difficulty getting him to use the hearing aids. He liked to take them off and use them as toys. His ability to walk and climb improved, and he became more active and adventuresome. His attention span was very short. At times it was difficult to keep him happily occupied. His main activity with toys was throwing them. He was seen by a consultant psychologist from the American Foundation for the Blind, who felt his behavior was well within normal limits for a deaf-blind child. During this period his mother took care of three foster children.

Fourth Year (3-4).—He continued to be very curious and to gain a full experience out of every activity. He was often found under the house or in some other hard-to-get-to place. He cooperated well with toilet training, and began feeding himself with a spoon. He drank from a cup without assistance. He sought more affection and reciprocated. For a month he was very interested in light switches. He became more and more independent in his play and he would climb on and off his rocking horse alone. In walking he liked to experiment, first walking on his toes, then on his heels and limping first on one leg and then the other. Toward the end of the year, after his baby sister was born, he became "impossible to handle." He was irritable and it was difficult to please him. He tried to make his wants known and would direct his mother to the cupboard for a cookie. He had great difficulty going to bed at night. He seemed frightened in bed. Finally his mother moved him into the same room with the older brother and put their beds together. His sleep problem disappeared. Occasionally he would reach over and touch his brother for reassurance.

Present Status (4 Years 6 Months).—In recent months he has seemed much happier. His attention span is longer. He is interested in how things work. He began swinging on any object he could hang onto. He learned to eat corn on the cob and to enjoy it.

An attempt was made to do more definitive hearing testing. He was reported to respond to music at 65 db. and to sound in a sound field through 80 db. A diagnosis of nerve-type deafness was reported.

He is enrolled in a play group for children with cerebral palsy. There was no other group that would accept him because of feelings about the complexity of the problem. At first he was unhappy being away from home for part of the day, and in a strange place. Gradually he has accepted the new environment and seems to enjoy being with the other children. An electroencephalogram done at this time was normal. His general health is good. It is interesting that this boy has always had periods of inactivity and irritability, which at first lasted two to three months at a time. Now these periods last only a week or a few days. After these difficult periods pass, he always seems happier, easier to handle, and capable of some new activity. His attention span, for any object or play activity, is longest in a familiar environment. In a new environment his curiosity seems to keep him constantly on the move as he investigates the entire area. He has to do this independently, and resists any intrusion or control.

He eats well, feeds himself well, and is toilet trained. He is easily disciplined and controlled. He is interested in people and enjoys being around children. He is generally very happy. His biggest deficit is in speech development. He has made little progress with speech to date, but it is anticipated that he will learn to talk. His hearing deficit is his major problem relative to ultimate school placement. Although his visual handicap is severe, he may have enough vision in his right eye to learn to read large prints. The ideal school placement will be hard to find. He may go to the State Residential School for the Blind, where there is a special program for deaf-blind children. On the other hand, he may be able to go to a daytime school for the deaf and get along with his limited vision.

Case 9.—This girl was born Jan. 6, 1952, nine weeks prematurely. Her birth weight was 3 lb. 6 oz. (1,530 gm.). Nothing is known of the mother's pregnancy or delivery, since she is an adopted child. The child was diagnosed as partially blind, owing to retrolental fibroplasia, at 6 months of age. It was apparent that she could see something at that age, in that her eyes made constant searching movements and she would look in the general direction of some brighter objects. It was reported that the upper nasal quadrants of the retina of each eye were involved symmetrically. The remainder of the retina appeared normal. At the present time she wears glasses to correct the myopia of -7Δ in the right eye, and $-10\frac{1}{2}\Delta$ in the left eye. With her glasses and using both eyes, her vision tests as 10/70. She is at present in the first grade, and reads from the regular first-grade primers. She is no longer classified as blind, al-

though the degree of vision she now has was not anticipated in the first year of her life.

The parents accepted this child for adoption when she was 2½ months of age. The child was not suspected of being blind at that time. They were obviously concerned when they did learn of her blindness when she was 6 months of age. The mother was silent and unexpressive and seemed overwhelmed. The father did most of the talking for the family during interviews, and seemed to be a stabilizing influence. This baby was obtained through an agency, and the agency gave the parents every opportunity to give the baby up if they felt they could not cope with the situation. Both the parents seemed to mature while caring for the child. In the long run the mother gave her the most warmth of affection and showed the most ingenuity in providing for this child's needs to promote good development. The family subsequently adopted a little boy from the same agency. He appears to be normal in every way.

First Year (0-1).—At 24 weeks of age she sat propped with her head steady, brought her hands together in the midline, laughed aloud, put toys in her mouth. She seemed to be functioning at about a 15-week level, which would be compatible with her age corrected for 9 weeks of prematurity. By 42 weeks of age she could sit without support indefinitely, stood holding onto the rail, held her own bottle, fed herself crackers, pivoted in the prone position. She would look at light, but otherwise her eyes seemed to wander. She was given a developmental age of 35 weeks. Her age corrected was 33 weeks; therefore she received a developmental quotient of 104.

At one year of age, in a pediatric clinic, there was considerable concern because of her small head circumference of 40½ cm. Her weight was 16 lb. 14 oz. (7,655 gm.). Though there were no abnormal neurological signs, her general progress was not considered normal in this clinic.

Second Year (1-2).—During the first six months of this year, her head continued to grow at a normal rate, though it was small. At 18 months of age her head circumference was 43 cm., her height 27½ inches, and weight was 20 lb. (9,070 gm.). She could walk across the room, up and down steps with her hands held; held her own cup; took off her shoes and socks on request. She was next seen for a play evaluation at 22 months of age. She walked rapidly, obviously using her vision to guide her. When she came to a dark spot on the floor, she stopped and shuffled her foot up to it to be sure she didn't trip over something. She said many words in Spanish, her parents' language, and some English. On verbal request she pointed to the parts of her body without error. She still had some searching movements of her eyes, but she could at times focus both together quite well. At that time it was still felt that she would have to learn Braille for reading.

Third Year (2-3).—During this year her language became quite fluent, though entirely in Spanish. She became toilet trained, but refused to feed herself with a spoon. In other ways she was independent and would go alone to visit her grandmother in the house next door. The second child, a normal boy, was adopted the end of this year.

Fourth Year (3-4).—In this year she started to learn English. Her Spanish language ability was the pride of the grandparents, for she was the only grandchild who would converse with them in Spanish. She was a sociable, enthusiastic child, and would work or play with complex items for long periods of time. She enjoyed books and stories. Toward the end of the year she accepted feeding herself with a spoon or fork.

Fifth Year (4-5).—In this year she became apprehensive in new situations and was afraid of strangers. Loud noises frightened her. At 4 years and 9 months she was seen by the psychologists for more formal testing. She was extremely apprehensive, and the introduction of a new activity was sufficient to make her break into tears. Her father was present during the testing and tended to push her to accept and try to test items. He seemed to attempt to deny that she had any visual handicap at all. The psychologists felt that in many instances her failures seemed to be due to her extreme anxiety. On the Hayes-Binet test she achieved a score of 82, but it was felt that her actual potential was probably better than this score would indicate. On the Vineland Social Maturity Scale her score was 98.

The end of this year she was enrolled in a parochial kindergarten.

Sixth Year (5-6).—At first she was very timid in school and cried a lot. Gradually she accepted the situation and came to like school.

Present Status (6 Years 3 Months).—She is attending the first grade in a Catholic school. She walks to school alone, and takes her lunch. She can read from the regular primer and copies written material from the blackboard, and has finished the first arithmetic book. She speaks Spanish and English well. Socially she seems much more confident. It is anticipated that she will continue to do well in school, although she may have difficulty later on with books with small print. Her general health is excellent.

CASE 10.—This boy was born June 6, 1954, nine weeks prematurely. His birth weight was 3 lb. 8 oz. (1,590 gm.). His mother had pyelonephritis in the last three weeks of her pregnancy, and a previous child had been born prematurely. Her delivery was normal. The boy was diagnosed as having retrolental fibroplasia at 2 months of age. Though his mother thought he had some vision early in

infancy, he had none when first seen and to date shows no evidence of vision. The first child in this family was also prematurely born, and also is blind as a result of retrolental fibroplasia. He is two years older than this boy. There is a younger child, a girl, born at term, who has normal vision. This boy had some physical difficulties in early infancy, primarily severe respiratory infection and pneumonia. In the past two years he has been in good health.

The mother of this boy was only 17 when her first son was born prematurely and was found to be blind. She was only 19 when this boy was born. She has never appeared well and complains of chronic fatigue. Despite her apparent ill health, she was indifferent toward medical care, even when this was urged on her, in an effort to prevent premature delivery of the second child. The family's financial means have been limited. The father works hard to support the family. The mother also works intermittently. The mother's seeming indifference and depressed attitude was a major source of frustration for all those who tried to work with her and to help her. Even when both boys were chronically ill with recurrent respiratory infections and had significant anemia, she remained apathetic toward medical care. Nevertheless her relationship to the children seemed to be very strong. Emotionally and socially, both the boys seemed to develop rapidly and with emotional strength. The frustation of working with this family made it difficult to see the positive contributions of both parents to these blind boys, but no one could deny they were there.

The maternal great-grandparents have played an active part in caring for the boys, and in aiding these parents. It is hard to evaluate their contribution.

First Year (0-1).—This boy was first seen for a developmental examination at 25 weeks of age, or a corrected age of 16 weeks. He did everything easily at a 16-week level, and many items at a 20-week level. The latter were pull to sit, with no head lag; prone, arms extended; precarious grasp of the cube; massed cubes, grasps one; squealing and pats the bottle while being fed. He was given a developmental age of 16 weeks, and a developmental quotient of 100. There was some consideration of scoring him higher than this.

At 7 months of age he was hospitalized with a diagnosis of pneumonia following a prolonged upper respiratory infection.

By 9 months of age he sat briefly without support, stood with hands held, held his own bottle, transferred objects from one hand to the other; and talked to his toys. He rubbed his eyes a great deal and would evert his eyelids. The intraocular tension in both eyes was said to be normal. He was kept in bed a great deal, but despite this seemed to develop well motor-wise.

Second Year (1-2).—At 15 months he could crawl; sit well without support; pull to a stand in a crib; walk with two hands held; play pat-a-cake. He related easily to people and enjoyed playing with his brother. However, he was very aggressive and would bite and pinch when he was thwarted. He always wanted his brother's toys.

He was seen for a play evaluation at 20 months of age. He walked everywhere holding onto furniture. He vocalized a great deal, using words and jargon. His vocabularly was about 20 words. His general manipulation of toys was good and he showed a great deal of curiosity. He was considered to be doing reasonably well. No abnormal neurological findings were noted. His head circumference was 46 cm. His mother compared him unfavorably with his older brother, who she thought developed more rapidly and was easier to manage.

Third Year (2-3).—At 25 months of age he started to walk alone and began to finger feed himself. He was seen for psychological testing at 28 months of age. A Vineland Social Maturity Test was done at that time and a score of 104 was given. By 30 months he was talking in phrases and indicated his toilet needs, but his mother did not follow through with toilet training. His language was well developed by 36 months, and his motor development was very good.

Fourth Year (3-4).—At 40 months of age his brother started school and he was home alone. Generally he stayed with his great-grandmother while his mother worked. He became less "stubborn" after his brother started school. He accepted toilet training, and his aggression decreased. He began to chatter constantly.

Present Status (4 Years).—At 4 years of age he was seen for psychological testing. His score on the Hayes-Binet test was 105, and on the Vineland Social Maturity Scale 115. His head circumference is 49 cm.

He is a very capable boy. He uses his hands well, learns to manipulate objects readily, and will follow directions. He is at ease with strangers and talks freely with them. His adjustment to all new situations is remarkable. His general health is good.

It is anticipated that he will attend the public school for the blind, where his brother attends. These parents were not particularly interested in a school program integrated with sighted children. They are very well satisfied with the older boy's school experience. This boy should do well in school.

Summary

Ten prematurely born children with normal vision and ten prematurely born children who were blind as the result of retrolental fibroplasia were evaluated in the

first year of life by means of the Gesell infant development test. All were considered to be developmentally normal at that time, although one of the blind children was found to have a severe hearing deficit in addition to his blindness. This article is concerned with the further development of these children in the subsequent four to five years.

Seven of the premature infants with normal vision were available for retesting by the Stanford-Binet intelligence test and the Vineland Social Maturity Scale and all were normal at 3 to 6 years of age.

Six of the blind children are doing very well as determined by biographical reports of their play activities and social responses and also by psychological testing. Two of these children have acquired a small amount of useful vision in one eye, and a third child has useful vision in both eyes and can read large print with glasses. The remaining three are essentially totally blind. The child with the double handicap of deafness and blindness is progressing surprisingly well and is believed to be normal in his mental potential. However, it is impossible to effectively evaluate his abilities. He has acquired useful vision in one eye that helps him considerably.

Three of the children are functioning at a mentally retarded level. However, all show some signs of reasonably normal development. All three have withdrawn considerably from social contact and have other behavioral difficulties suggestive of severe emotional problems. It was concluded that they probably have normal mental potential that is not manifest because of severe emotional problems. Two are receiving psychiatric help and have shown some improvement.

Neurological examinations did not reveal any abnormalities in any of the children, except the deaf child. Electroencephalograms were done on six of the children and were not diagnostically significant, though two were suggestively abnormal.

A tabulation of the development of four self-help items—(1) walking without support; (2) feeding self with spoon; (3) talking in sentences; (4) toilet training—revealed some delay in the development of all except talking. This pertains to the six normal children, and those with some useful vision were not advanced over those without vision on these items. The three functionally retarded children did almost as well as the other children with respect to walking but had not had success with any of the other items by age 4.

It was concluded that developmental examination in the first year of life is a valuable adjunct in the evaluation of prematurely born blind children. This is of particular value to the parents of blind children and the professional workers who aid the parents.

The biographical summaries reveal some of the details of the development of the individual children and the family problems associated with rearing a blind child.

We are grateful to the staff of the Field Service for Blind Preschool Children of the California School for the Blind, especially Mrs. Margery Cutsforth, Mrs. Elaine Kapanen, Mrs. Dorcus Douglass, and Miss Claire Jackson, who is now with the Dallas Services for Blind Children, for their continuous cooperation and very carefully recorded observations. We also wish to express our appreciation to the staff of the Holy Family Adoption Service for their help and cooperation.

Department of Pediatrics, University of California Medical Center (24).

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Retrograde Aortography in Corrected Transposition of the Great Vessels

OTTO G. THILENIUS, M.D.; ELEANOR LU, M.D.; FRANCESCO S. TOLONE, M.D., and DONALD E. CASSELS, M.D., Chicago

In relation to congenital heart diseases the term "transposition" usually applies to abnormality of position of the aorta and pulmonary artery, transposition of the great vessels. However, the term "transposition" can also be applied to the situation when aorta and pulmonary artery arise from their proper physiological ventricles, but the ventricles are anatomically transposed. In this case the right ventricle has the internal anatomical characteristics of the left ventricle, the left ventricle those of the right (Fig. 1). This is commonly referred to as corrected transposition, although this is an inadequate descriptive term. The anatomical and clinical features as well as the surgical implications of this malformation have been described.[1-11] This abnormality is not as infrequent as formerly believed. The radiological characteristics of corrected transposition have either not been appreciated or have been misinterpreted as truncus arteriosus, tetralogy of Fallot, ventricular septal or other defects, depending on the symptomatology caused by the associated defects. The roentgenological findings of corrected transposition on the chest film during cardiac catheterization and angiocardiography have been reported in the past.[1,8] It is the purpose of this communication to describe the typical appearance of corrected transposition as demonstrated by retrograde aortography. Two characteristic instances of corrected transposition were selected as illustrative of the diagnostic problem.

Submitted for publication Nov. 28, 1958.

From the Departments of Pediatrics and Radiology, University of Chicago Clinics.

Report of Cases

CASE 1.—A boy, 11 years 7 months old, has had cyanosis and a heart murmur since birth. Clubbing of fingers and toes was noted at 18 months. Angiocardiogram at 4 years of age was interpreted as characteristic of truncus arteriosus. Physical examination revealed marked cyanosis and clubbing, cardiomegaly, systolic thrill, and Grade 4 systolic murmur over the precordium, maximum at second intercostal space at the left sternal border. Electrocardiogram showed right ventricular hypertrophy. Roentgenogram of thorax (Fig. 5) showed cardiomegaly and convex left heart border. Retrograde aortogram (Fig. 6) demonstrated that the ascending aorta formed the left upper border of the heart, which is characteristic of corrected transposition of great vessels. Exploratory thoracotomy showed presence of an auricular septal defect, a large ventricular septal defect, hypoplastic pulmonary artery, and a stenotic tricuspid left atrioventricular valve. Corrected transposition of the great vessels was confirmed.

CASE 2.—A girl, 6½ years old, has had moderate dyspnea on exertion and recurrent heart failure since birth. Physical examination revealed prominent precordial bulge and substernal pulsation, cardiomegaly, a Grade 3 systolic murmur in the left second intercostal space, a continuous murmur in the right second intercostal space, and an apical diastolic murmur. Electrocardiogram showed combined ventricular hypertrophy. Dye dilution curve showed a left-to-right shunt. Roentgenogram of the thorax revealed cardiomegaly, enlarged left auricle, and increased pulmonary vascularization. Retrograde aortogram (Fig. 7) demonstrated abnormal position of the ascending aorta and inverted coronary arteries. Diagnosis of acyanotic congenital heart disease with auricular and ventricular septal defects, corrected transposition of great vessels, and patent ductus arteriosus was made. Repair of the ventricular septal defect and ligation of ductus were performed with the aid of extracorporal circulation. Patient died 20 hours after the operation. Autopsy confirmed preoperative diagnosis.

Cardell[2] differentiates four types of corrected transposition. According to his

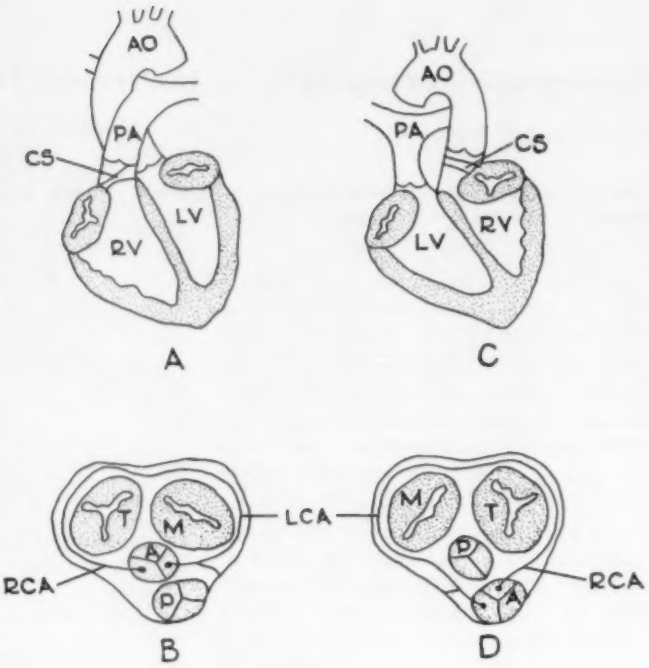


Fig. 1.—Diagrammatic representation of the ventricles and the great vessels in normal (*A, B*) and in corrected transposition of great vessels (*C, D*). *A* and *C*, anterior view. *B* and *D*, cross sections viewed from above. *CS*, crista supraventricularis. *RCA* and *LCA*, right and left coronary artery.

classification, both reported cases are Type B3, which is transposition with bulboventricular inversion. This type occurs most frequently. Figure 1 demonstrates its anatomical characteristics.

Figures 2-4 demonstrate three variations of the aortic root and arch for comparative purposes. This is of importance to emphasize the abnormal origin of the root of the aorta in corrected transposition. Figure

Fig. 2.—Angiocardiogram of a one-year-old child illustrating the opacified left ventricle and a normal aortic arch. The aorta ascends medially and posteriorly to the pulmonary artery, and the arch projects to the left.

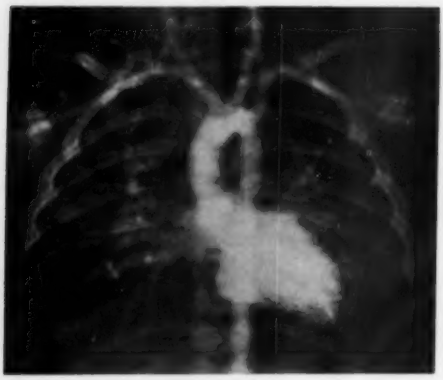


Fig. 3.—Retrograde aortogram showing a normal aortic arch in a three-month-old infant. The aorta ascends toward the right and arches posteriorly.

Fig. 4.—Roentgenogram of the thorax of a 17-year-old girl with a right aortic arch. The superior mediastinum lies chiefly to the right of the midline, and the mediastinal shadow is absent on the left.

Fig. 5 (Case 1).—Roentgenogram demonstrating the characteristic convex left upper heart border.

2 shows a normal left aortic arch in childhood and Figure 3 a normal left aortic arch in infancy. In the latter the aorta arches posteriorly in the sagittal plane. Figure 4 is the silhouette of a right aortic arch. In each of these variations the ascending aorta is in a medial position and is not in relation to the left border of the heart.

In corrected transposition the cardiac silhouette shows the left heart border either unusually straight or slightly bulging in the area normally occupied by the pulmonary artery [1,5] (Fig. 5). This silhouette is typical for corrected transposition but not pathognomonic. The catheter in the ascending aorta shows displacement to the left heart border. The retrograde aortogram clarifies the cardiac silhouette (Figs. 6, 7). The aorta arises far to the left of its normal origin. In each of the two instances there

Fig. 6 (Case 1).—Retrograde aortogram. The ascending aorta forms the upper left border of the heart.

Fig. 7 (Case 2).—Retrograde aortogram showing the characteristic position of the ascending aorta and the inverted coronary arteries.

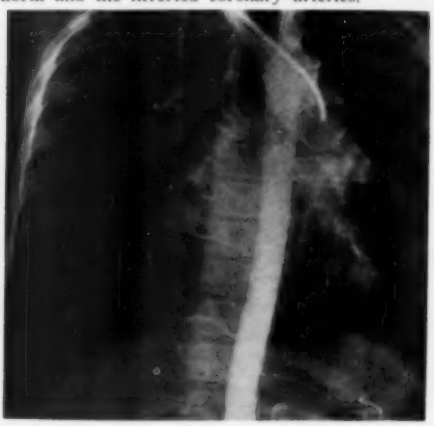


Figure 7

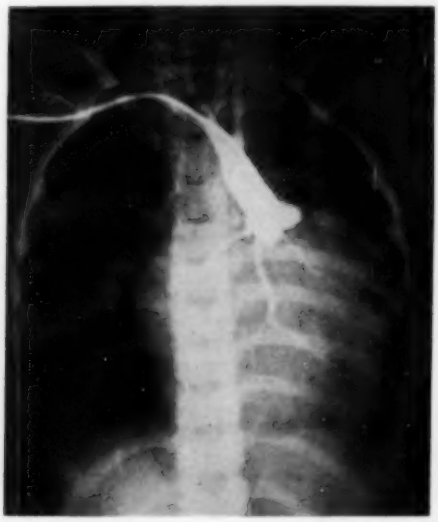
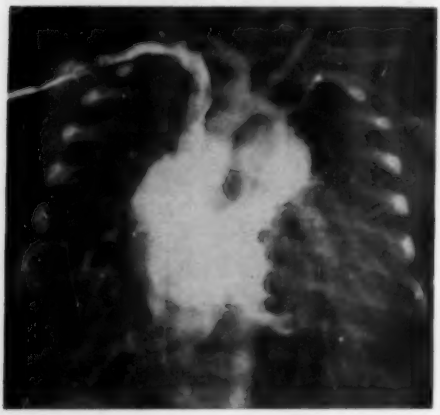


Fig. 8.—Specimen of a case of corrected transposition of great vessels. Anterior view. The right or venous ventricle, which morphologically is the left ventricle, is supplied by the left coronary artery and its branches.

is a left aortic arch. A right aortic arch, however, also occurs in association with corrected transposition. Regardless whether the arch is right or left the root of the aorta in corrected transposition appears in the same typical lateral position.

The aortogram also demonstrates the abnormal pattern of the coronary arteries. In corrected transposition the coronary arteries accompany their proper anatomical ventricles. As the ventricles are inverted the coronary arteries are also inverted. That is, the left coronary artery with its anterior descending and circumflex branch is on the right side and the right coronary artery with its posterior descending and circumflex branch is on the left. Figure 6 illustrates such a left coronary artery of the right-sided, morphologic left ventricle by aortogram, and Figure 8 shows a pathologic specimen. This coronary artery is considerably larger than the normal coronary vessel of the pulmonary ventricle. The size of this vessel of the low-pressure ventricle can cause considerable difficulties during open heart surgery by limiting the extent of the incision.

Fig. 9.—Angiocardiogram of a 3-week-old infant with complete transposition of the aorta and levoposition of the pulmonary artery (Taussig-Bing heart) demonstrating the aortic root to the right of the pulmonary artery.



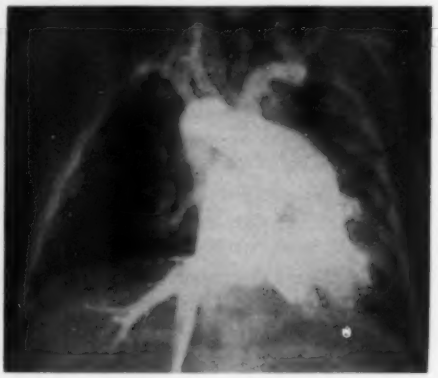


Fig. 10.—Angiocardiogram of a 4-month-old infant with extreme hypoplasia of the pulmonary artery and large aorta. Both vessels arise from their proper ventricles in normal fashion.

Comment

Corrected transposition has so far been diagnosed intra vitam by either angiocardiogram [1] or by cardiac catheterization.[5] In the latter the catheter is in an abnormal medial position in the pulmonary artery during right heart catheterization. In the above-described instances of corrected transposition the final diagnosis had not been expected originally. The aortograms were rather done while searching for a patent ductus arteriosus, as unusual pulsations of the "pulmonic" area of the left heart border as well as murmurs compatible with though

not typical of such a diagnosis had been noted. In both instances the aortogram gave conclusive information in regard to the diagnosis of corrected transposition though it naturally was not helpful in defining associated intracardiac defects.

Corrected transposition is probably more often diagnosed either by cardiac catheterization or angiocardiography. The reason for this is that the variety of associated cardiac malformations determine the clinical picture. However, the retrograde aortogram appears superior to the angiogram in the diagnosis of corrected transposition as it shows clearly (1) the abnormal position of the root of the aorta, uncovered by shadows due to filling of other chambers of the heart; (2) the typical inverted pattern of the coronary arteries.

Two points of differential diagnostic interest should be mentioned. As corrected transposition is at times associated with marked cyanosis, the differential diagnosis has to be made between complete and corrected transposition, as the surgical considerations are different. Here the position of the aortic root differentiates the two conditions. In complete transposition the aorta is anterior but does not arise along the left heart border. This point is well demonstrated by Figure 9, an angiogram of a Taussig-Bing syndrome, which shows the root of the transposed aorta arising from the right ventricle medially. The coronary arteries are not inverted as in corrected transposition.

The second condition of differential diagnostic interest cannot be clarified by angiocardiogram. Figure 10 is the angiocardiogram of a 4-month-old infant who was cyanotic from birth. The appearance of the aortic root suggests corrected transposition. The infant died 28 hours after surgical exploration. The autopsy revealed a wide aorta arising in normal position from a normal left ventricle. The right ventricle was hyperplastic, and the pulmonary artery only about 1 mm. in diameter. Additional findings were a patent foramen ovale, a small ventricular septal defect high in the muscular septum, large bronchial arteries, and complete absence of the ductus arteriosus. The abnormal origin of the aortic root as demonstrated by the angiocardiogram was due to abnormal position of the heart in the chest. The ascending aorta in this apparent position in the absence of the anatomical complex of corrected transposition is uncommon.

It is evident that the characteristic findings of the corrected transposition can be demonstrated only on frontal but not oblique or sagittal aortography.

Summary and Conclusion

The characteristic lateral displacement of the root of the aorta in corrected transposition was demonstrated by retrograde aortography.

When this diagnosis requires confirmation, the retrograde aortogram appears to be nearly pathognomonic.

Division of Pediatrics, University of Chicago Clinics (37).

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Infantile Pyknocytosis

A Common Erythrocyte Abnormality of the First Trimester

PHILOMENA TUFFY, M.B., Ch.B.; AUDREY K. BROWN, M.D., and WOLF W. ZUELZER, M.D., Detroit

In the course of an intensive study of full-term newborn infants manifesting hyperbilirubinemia in the absence of hemolytic disease, we became aware of the occurrence of markedly distorted and contracted erythrocytes in the blood of some of these patients. These cells conform to the type previously described under a variety of names, such as "burr cells," [1] "irregularly distorted and contracted erythrocytes," [2] and others. In order to evaluate the significance of these cells it became necessary to determine whether and in what percentage they might normally be found in this age group. We therefore studied unselected full-term and premature infants as well as adults. A significant age-determined relationship was found in that burr cells were encountered in slightly greater numbers in healthy full-term infants than in adults, and in significantly greater numbers in prematures than in full-term infants. Where the number of burr cells was within the physiologic range thus established by us, there were no recognizable signs of increased hemolysis, although this does not preclude the possibility that a minimal hemolytic process not detected by ordinary methods was in fact taking place. Having thus gained an impression of the limits of the phenomenon in the apparently normal infant, we were able to delineate a hematologic entity characterized by a significant increase in the number of burr cells and associated with an obvious hemolytic anemia, in 11 otherwise normal infants in the first three months of life. It is the purpose of this paper to describe the spectrum of these hematologic states.

Submitted for publication April 24, 1959.

From the Child Research Center of Michigan, Children's Hospital of Michigan, and the Department of Pediatrics, Wayne State University College of Medicine.

This work was supported by grants from the National Institutes of Health (RG-5105), the Children's Leukemia Foundation of Michigan, and the Cerebral Palsy Fund, Lambda Tau Delta.

Case Material

The following groups were investigated:

1. Forty unselected healthy adults for control purposes.

2. One hundred two unselected full-term infants 2-3 days of age. Of these 31 were white and 71 Negro; 46 of these infants were also available for follow-up studies at 6-8 weeks of age.

3. Sixty unselected premature infants whose ages ranged from 1-84 days.

4. Forty-three full-term infants, twenty-four white and nineteen Negro, who were studied because of an unexplained hyperbilirubinemia. (Hyperbilirubinemia for the purpose of this study as applied to full-term infants was defined as a serum bilirubin level in excess of 12 mg. %.) In all of these cases Rh and ABO hemolytic disease, congenital spherocytosis, and toxic hemolytic anemias were ruled out by appropriate studies, as were organic liver disease, atresia of the biliary tract, sepsis, and viral infections. Of this group, 13 infants (6 white, 7 Negro) who did not require exchange transfusion were available for follow-up, together with 7 infants who had received an exchange transfusion.

5. Seven infants manifesting an acute hemolytic anemia in the first few weeks of life.

Methods

The number of "burr cells" was determined by counting 1,000 red cells on a Wright's stained smear.

Heinz body preparations were made by supravital staining with brilliant cresyl blue and in some instances also by examination of supravitally stained wet drops. Hematologic data were obtained by the usual standard procedures. Bilirubin de-

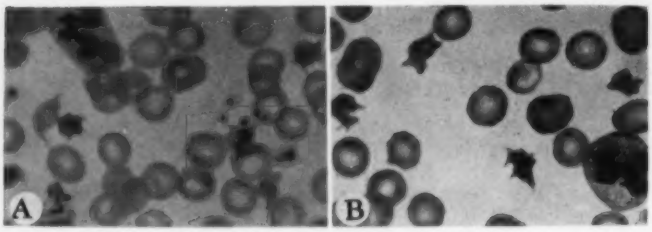

Fig. 1.—Typical pyknocytes (burr cells). (*A*) Normal premature infant (age 5 weeks). (*B*) Infantile pyknocytosis (Patient 4, age 7 weeks). Blood film taken at the time of mainfest hemolytic anemia.

terminations were done by the modified method of Powell.[8]

Erythrocyte reduced glutathione determinations were done by the method of Grunert and Phillips[4]; the glutathione stability test by the method of Beutler[5]; and the glucose-6-phosphate dehydrogenase content by the method described by Zinkham, Lenhard, and Childs.[6]

Paper hemoglobin electrophoresis was carried out by the method described by Zuelzer, Neel, and Robinson.[7]

Fetal hemoglobin determinations were done by the Singer method of alkali denaturation.[8]

The following liver function tests comprised the liver spectrum: total protein, albumin-globulin ratio, cephalin flocculation, and thymol turbidity tests. These were done by standard methods. The serum glutamic oxaloacetic transaminase was done by the method of Cabaud, Leeper, and Wroblewski.[9]

Observations

In dry-stained preparations, the type of cell with which this report is concerned appears as a much distorted, completely irregular, densely stained erythrocyte, usually appreciably smaller than the undistorted cells, and having from several to many spiny projections (Figs. 1, 5, 6). We were as much impressed with the density of these cells and their resemblance in this respect to spherocytes as we were with the irregularity of their shape, and for this as well as other reasons, which will be presented later in this report, we shall refer to them hereafter as "pyknocytes."

1. *Normal Full-Term Infants.*—In the adult control cases, pyknocytes never constituted more than 0.3% and in most instances were completely absent, in keeping with the observations of Schwartz and Motto.[1] However, in the 102 unselected full-term healthy infants whose blood films were examined in the first few days of life, the number of pyknocytes ranged from 0.3% to 1.9%.

In the majority of these infants the percentage of pyknocytes in the immediate newborn period was between 0.3% and 0.5%. The blood of those infants who could be reexamined at five to eight weeks showed more than 0.5% pyknocytes in the vast majority of cases and nearly half of the infants in that age group had 1.0% or more (Fig. 2). No further follow-up

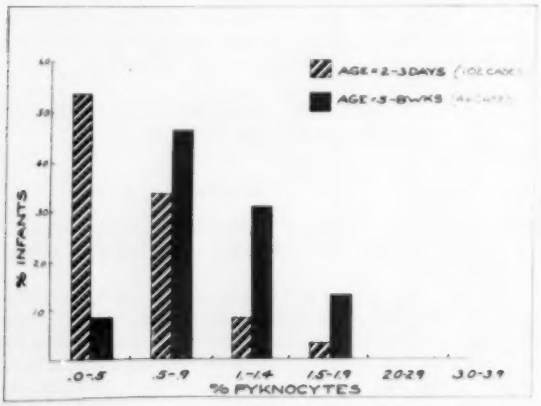

Fig. 2.—Pyknocyte count in normal full-term infants. Comparison of values at age 2-3 days and at 5-8 weeks.

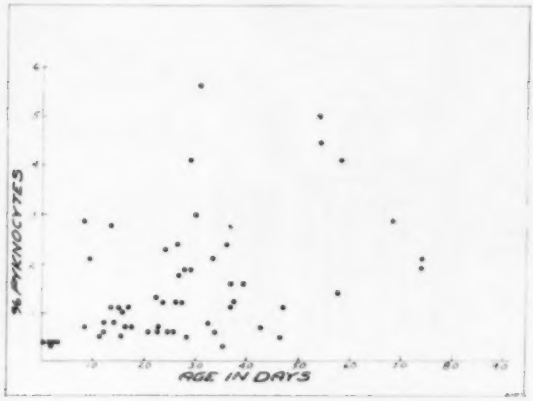

Fig. 3.—Pyknocyte count in 59 normal premature infants. Each dot represents a single infant.

of these infants was possible. We have not ascertained the age when the normal adult pattern was established, but from a survey of many blood films of infants of various ages we have gained the impression that pyknocytosis rapidly decreases after the second or third month.

2. *Premature Infants.*—The premature infants as a group were found to have greater numbers of pyknocytes as compared with full-term infants, the range being from 0.3% to 5.6% (Fig. 3). The age of the premature infants in the group studied ranged from 1 to 84 days. The findings indicated that in this group, too, there was a tendency toward an increase in the number of pyknocytes with increasing age (Fig. 4). But in this group, serial follow-up of the individual cases was not possible.

In neither the full-term nor the premature infants was there any correlation with reticulocytosis, increased bilirubin levels, serological incompatibility between mother and child, history, or abnormal physical or laboratory findings.

3. *Infants with Pyknocytosis.*—There were 11 such cases (Table). All but one of these came to our attention within a period of two years. Increased numbers of pyknocytes were found in 4 of the 43 infants studied primarily because of hyperbilirubinemia not explained by hemolytic disease or recognizable organic liver disease. In one of these, an infant whose condition was thought to warrant an exchange transfusion at 2½ days of age, the hematologic status following this procedure could not be evaluated. In the remainder a manifest hemolytic

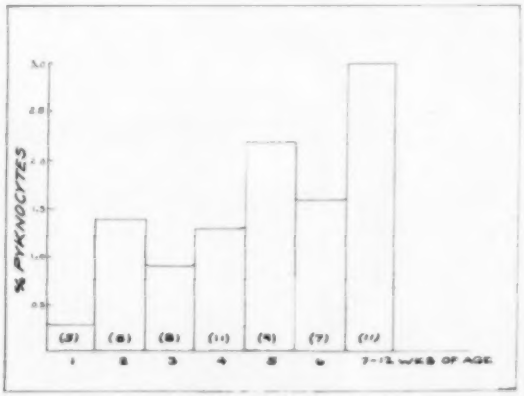

Fig. 4.—Average pyknocyte count in normal premature infants from birth to 12 weeks of age.

Summary of Pertinent Findings on Cases of Infantile Pyknocytosis

	Clinical Data					
Patient	Age on Admission, Days	Sex	Race	Birth Weight, Gms	Chief Complaint	Physical Examination
1	1	F	W *	2,920	Jaundice soon after birth	Liver 2.5 cm.; spleen 3.5 cm.
2	1.5	M	W *	3,459	Jaundice at 18 hours of life	Liver 3 cm.; spleen 2.5 cm.
3	1	M	W	3,487	Jaundice in 1st 24 hr. of life	
3	22				Pallor	Liver 1-2 cm.; spleen tip felt
4	2.5	M	N	3,232	Jaundice on 2d day of life	No hepatosplenomegaly
4	52				Anemia	
5	13	F	W *	3,274	Jaundice since 1st few days of life	Liver 2.5 cm.; spleen 0.5 cm.
6	18	M	W	2,098	Persistent jaundice since 1st day of life	Liver edge palpable
7	18	F	W	2,892	Anemia and pallor since 1st 24 hr. of life; history of neonatal jaundice	Liver 2 cm.; spleen 1 cm.
8	23	F	W	2,580	Pallor; jaundice of 1 day's duration	Liver 2-3 cm.; tip of spleen felt
9	26	F	W	2,636	Pallor of 2 days' duration	Tip of spleen palpable
10	20	M	W	1,843	Jaundice of 2 days' duration	Tip of spleen palpable
11	24	M	W	1,588	Pallor of 2-3 days' duration	No hepatosplenomegaly

* Jewish.

Summary of Pertinent Findings on Cases of Infantile Pyknocytosis (Continued)

Patient	Hemogram								Fragilities			Typing				Coombs Test		
																Direct	Indirect	
	Hemoglobin, Gm. %	Reticulocytes, %	WBC	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Heinz Body Preparation	Pyknocytes, %	Mechanical	Osmotic	Mother		Infant			Mother's Serum with Infant's Cells	Mother's Serum with Panocells
1	12.3	10.2						Neg.	50.0		Slightly decreased †	AB	CDe	A	CDe	Neg.	Neg.	
2	17.0	3.8	24,600	36	58	3	3	Neg.	6.0			A	CDe	A	CDe	Neg.	Neg.	
3	15.7	9.3						Neg.	1.4			A	CDe	A	CDe	Neg.	Neg.	
3	7.0	11.0							17.3	19.1	Increased					Neg.	Neg.	
4	17.0	5.6							1.4			B	cDe	B	cDe	Neg.	Neg.	
4	8.5	5.4							9.6									
5	9.7	2.2	14,600	41	57	2		Neg.	5.7	9.5	Slightly decreased	AB	CDe	B	CDe	Neg.	Neg.	
6	7.1	15.0						Neg.	5.0 ‡	5.7 ‡	Normal ‡	O	CDe	O	cde	Neg.	Neg.	
7	4.9	21.9	58,000					Pos.	33.3			O	CDe	O	cde	Neg.	Neg.	
8	4.6	15.7	50,000	37	58	5		Neg.	25.8	5.6 §	Slightly decreased §	A_1	CDe	A_1	CDe	Neg.	Neg.	
9	5.6	13.5	19,650	38	49	6	7	Neg.	9.8			A	CDe	B	cde	Neg.	Neg.	Neg.
10	6.6	15.0	21,800	42	52	4	3	Neg.	18.7	11.7 ‡	Slightly decreased ‡	B	cDe	O	CDe	Neg.	Neg.	Neg.
11	5.8	22.1	33,600	48	46	4	2	Neg.	29.8			A_1	CDe	A_1	CDe	Neg.	Neg.	

† After exchange transfusion.
‡ After transfusion.
§ 4 weeks after transfusion.

Summary of Pertinent Findings on Cases of Infantile Pyknocytosis (Continued)

Patient	Other Laboratory Findings								Special Studies					
											Erythrocyte Reduced Glutathione			
	Total Bilirubin, Mg. %	Direct Bilirubin, Mg. %	"Liver Spectrum"	Transaminase (SGOT), Units	Urinalysis	BUN, Mg. %	Blood Culture	Marzini	Hemoglobin Electrophoresis	Fetal Hemoglobin, %	Content, Mg. %	Stability ‖ Mg. %	Protection with Glucose	Glucose-6-Phosphate Dehydrogenase, Units
1	21.2	0.6			Normal		No growth	Neg.	AF		62.4	46.0	Partial (68%)	95
2	20.3	0.2 (2½ days)	Normal	85	Normal		No growth	Neg.						
3	7.8	0.2			Normal		No growth	Neg.						
3	1.5	0.1	Normal	50					AF	34.8				
4	15.4	0.2					No growth	Neg.	¶					
4														
5	20.3	0.6	Normal	70	Normal		No growth	Neg.	AF	54.6				
6	14.0	0.0	Normal	110 (at 6 weeks)	Normal	10.5	No growth	Neg.	AF	2.1 ‡	62.6	51.6	Complete	340
7	2.6	0.2	Normal	135	Normal		No growth	Neg.			58.0	41.4	Complete	570
8	7.4	0.2	Normal	235	Normal	12.2	No growth	Neg.	A	13.1 ‡	84.0	75.1	Complete	243
9	0.3		Normal		Normal		No growth	Neg.	AF	32.4	72.7	62.0	Complete	
10	17.8	0.9	Normal	257	Normal	19.6 13.0	No growth	Neg.	AF	56.5				
11	0.8	0.05			Normal		No growth	Neg.	AF		91.5	75.4	Complete	189

‖ After incubation with acetylphenylhydrazine.
¶ Sickle cell preparation negative.

anemia developed, and the entire group of four will therefore be described together with the seven infants who came to our attention primarily because of hemolytic anemia in the first two months of life, the presence and intensity of jaundice not being a valid criterion for making a distinction between these two groups.

In 7 of the 11 infants with abnormal degrees of pyknocytosis, the onset was in the immediate neonatal period with jaundice as the presenting symptom. In the severest case (Patient 1), the clinical picture simulated hemolytic disease with significant anemia, reticulocytosis, severe jaundice, and splenomegaly. In this patient nearly 50% of the red corpuscles showed the characteristic distortion on the first day of life. At 21 hours, the bilirubin level of the serum was 21.2 mg. %, and the patient received an exchange transfusion. Interestingly enough, after an exchange of 440 ml. of whole blood, the majority of the red corpuscles were again found to be pyknocytes, a fact which could not be explained by the production of new abnormal erythrocytes by the patient. We were thus led to assume that an extracorpuscular mechanism might affect the donor cells in vivo in a manner similar to its effect on the patient's own corpuscles, but we were not able to demonstrate such a mechanism in vitro by incubation of normal adult erythrocytes in the patient's serum under a variety of conditions. Over a period of months the percentage of pyknocytes in the patient's blood gradually decreased. At 6 months of age she had a normal blood picture, and her subsequent development was normal.

In a second infant (Patient 2), neonatal jaundice was equally severe and was likewise taken as an indication for exchange transfusion, but the erythrocyte abnormality prior to this procedure was far less marked than in the first patient (only 6% pyknocytes), and the only indication of a possible hemolytic process was the early development of such a marked degree of icterus. After exchange transfusion at 2½ days, the abnormal cells were no longer evident. The patient made an uneventful recovery and unfortunately was lost to follow-up.

The five other infants with jaundice in the immediate neonatal period all developed progressive anemia in the succeeding weeks. Only two of these came to our attention within the first two days of life, and neither of them had appreciable pyknocytosis or anemia at that time, but both developed pyknocytosis pari passu with their anemia. In one of these (Patient 3), 17% of the erythrocytes showed the deformity at 3 weeks of age, by which time the hemoglobin had fallen to 7 gm. % with 11% reticulocytes. In the other infant (Patient 4), the pyknocytosis was less marked, and a hemoglobin level of 8.5 gm. was reached only at 7 weeks of age.

The remaining three patients with neonatal jaundice (Patients 5, 6, 7) were not seen by us until they were between 2 and 4 weeks of age, but in each case there was a history of severe and prolonged neonatal jaundice, and two of them were still jaundiced when seen by us, with bilirubin levels of 20.3 and 14.0 mg. %, at 13 and 18 days respectively. All three had significant degrees of anemia and pyknocytosis, and two exhibited reticulocytosis as well.

Of the total group of 11 infants with pyknocytosis, 2 were never significantly jaundiced while 2 others who had shown no undue icterus in the immediate neonatal period, developed jaundice at about 3 weeks of age. Three of these four infants were prematurely born. The other was a full-term infant. Their blood picture at approximately 3 weeks of age did not differ significantly from that of the infants with pyknocytosis who had been initially jaundiced. Thus in all instances in which the development of the characteristic sequence was not interfered with by exchange transfusions, the pyknocytosis and hemolytic anemia were progressive after the neonatal period and reached a more or less severe stage by 3 weeks. The hemoglobin levels in this period ranged from 4.6-9.7 gm. %,

and the pyknocyte count from 5%-33%. There was a fairly good degree of correlation between the intensity of the pyknocytosis and the severity of the anemia. In most instances there was marked reticulocytosis. In only one of the patients (Patient 7) was it possible to demonstrate Heinz bodies. Special studies included erythrocyte glutathione levels and glucose-6-phosphate dehydrogenase activity. Results were normal for the age group in five of the six cases so studied. Hemoglobin electrophoretic studies were normal. Osmotic fragility of the erythrocytes was investigated in six cases. No characteristic pattern emerged. One infant (Patient 3) had a distinctly increased osmotic as well as mechanical fragility. In four cases the osmotic fragility was somewhat decreased, a phenomenon probably related to the hyperbilirubinemia. In two of these there was also evidence that a small percentage of the erythrocyte population showed a slight increase in osmotic fragility. Mechanical fragility was increased in three of the five cases in which it was done.

In each case there was a more or less marked leukocytosis, the white counts ranging from 14,600 to 58,000. The differential counts were not unusual for the age group. The platelets appeared normal in number and appearance.

Clinically there were no symptoms other than those attributable to the anemia. In all but two infants the spleen was enlarged, usually to a moderate degree, and most of the infants exhibited hepatomegaly. Except for the variable degree of jaundice and pallor, there were no other consistent physical findings.

With the exception of elevated transaminase in four of the seven cases so studied, there was no laboratory evidence of liver damage or impaired liver function, nor was there indication of renal disease or nitrogen retention on the basis of some other mechanism in any of the patients. All of the infants received simple transfusions as the sole form of therapy for anemia. Frequently the anemia recurred as the hemolysis persisted and pyknocytes continued to be present so that several weeks later it was necessary to give additional transfusions, but thereafter the process subsided and in each instance the pyknocytosis had disappeared by the age of 4 months, and eventual recovery was complete.

In no instance could a history of drug ingestion by either mother or child be elicited. In the case of Patient 1, sulfadiazine was administered three times, but in each instance the pyknocytosis and hemolysis were present before such therapy was instituted. Serologic incompatibilities between mother and child which might lead to hemolytic disease were excluded in every case.

The parents were studied in five cases and no abnormality of the erythrocytes could be detected. Two of the patients (6 and 7) were siblings, however, one male and the other female. The clinical course and blood picture were remarkably similar. Both developed early neonatal jaundice, which persisted for several weeks with high levels of indirect reacting serum bilirubin. Both had severe anemia at about 3 weeks of age, and their peripheral blood contained large numbers of pyknocytes and showed reticulocytosis. Each had a palpable spleen. Liver function tests were normal, but both had elevated serum glutamic-oxaloacetic transaminase levels. In another case (Case 5) the family history suggested that two previous siblings may have had the same condition as the patient. Both had been full-term infants with hyperbilirubinemia for which no explanation had been apparent at the time. One of these siblings had been jaundiced until 2 weeks of age, the other had died at 7 days of age.

A noteworthy feature of the group was that among 11 cases, 3, representing three families, were of Jewish origin. In one of these (Case 1), which happened to be the severest, with onset at birth, consanguinity of the parents was established. Only 1 of the 11 infants was Negro. Both the high incidence of Jewish infants and the low incidence of Negro infants are in contrast to the composition of this age group in the

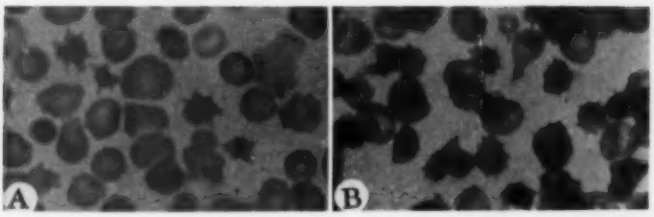

Fig. 5.—Infantile pyknocytosis (Patient 1). (*A*) Blood film obtained *prior* to exchange transfusion at age 1½ days. (*B*) Blood film one day *after* exchange transfusion.

population of our hospital. Representative case reports follow.

Report of Cases

CASE 1.—A full-term white female infant of Jewish descent whose parents were consanguineous. Her birth weight was 2,920 gm. There was no history of exposure to drugs in the mother. Pregnancy and delivery had been normal and respirations were spontaneous. There was no cyanosis. Jaundice was noted shortly after delivery, and on admission to The Children's Hospital of Michigan at 21 hours of age the infant was markedly icteric. The liver was palpable 2.5 cm. below the right costal margin; the spleen was felt 3.5 cm. below the left costal margin. There were no other abnormal physical findings.

Laboratory Findings.—The hemoglobin was 12.3 gm. %, and the reticulocytes were 10.2%. The peripheral blood smear showed about 50% very bizarre erythrocytes, which were distorted, deeply stained, and had several spiny projections along the periphery (Fig. 5, *a*). There was also marked polychromasia and many nucleated red blood cells, as well as some spherocytes on the peripheral blood smear. The total bilirubin was 21.2 mg. % with 0.6 mg. % direct reacting. The urinalysis was normal. The infant's blood type was group A, Rh-positive (CDe), and mother's type was AB, Rh-positive (CDe). The direct Coombs test was negative, and the indirect Coombs test (mother's serum with infant cells, with ACDE cells, with OCDE, and with father's cells) was also negative.

Course.—Because of the early elevation of the indirect bilirubin in the serum, in the presence of an obvious hemolytic process an exchange transfusion was done at 26 hours of age, using type-specific blood. Following exchange transfusion, a reticulocytosis of 18.9-21.2% was maintained for four to five days, after which time the reticulocytes decreased to 10%. The peripheral blood smear on the days immediately following the exchange transfusion again showed large numbers (62%-38%) of bizarre erythrocytes (Fig. 5, *b*). The serum bilirubin showed a postexchange rebound to 18.75 mg. % indirect, and 0.51 mg. % direct, and subsequently decreased progressively. After exchange transfusion, the infant was given sulfadiazine prophylactically for five days and discharged home with a hemoglobin of 11.5 gm. %.

At one month of age her hemoglobin was 7 gm. %, and reticulocytes were 17%. There were still large numbers of pyknocytes on the peripheral blood smear. She was readmitted to the hospital. The bilirubin on this admission was 0.33 mg. % total with 0.1 mg. % direct reacting. Urinalysis was normal except for one episode of gross hematuria on the second hospital day. She was transfused three times with packed red cells and was discharged after seven days when her hemoglobin was 11 gm. % and reticulocytes were still 10%. During this admission she developed diarrhea and received sulfadiazine.

Eight days later, at the age of 6 weeks, she was readmitted with bronchopneumonia. The hemoglobin had fallen to 9.3 gm. %. In a few days the hemoglobin dropped to 7.7; the reticulocytes were 4.4%. She was again given three packed-cell transfusions and was treated with sulfadiazine and oxytetracycline (Terramycin) for her infection. After 12 days she was discharged home with a hemoglobin of 11 gm. %.

At 3½ months of age her hemoglobin was 9.8 gm. % with 4% reticulocytes. Very few abnormal erythrocytes were present on the peripheral blood smear. When seen again at age 6 months, the in-

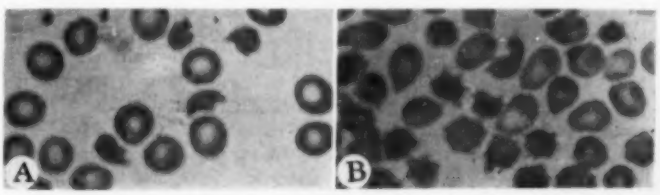

Fig. 6.—Infantile pyknocytosis in siblings. (*A*) Patient 6 (age 6 weeks). (*B*) Patient 7 (age 18 days).

fant was completely normal in every respect, and there was normal red cell morphology.

Her subsequent course has been uneventful, and her growth and development at the present time (age 5 years) is normal. Recently it has been possible to establish that her erythrocyte glucose-6-phosphate dehydrogenase is distinctly lower than normal (95 units). While her red cell reduced glutathione level is not low (62 mg. %), there is some instability of the glutathione when acetylphenylhydrazine is incubated in vitro with her red cells. This instability is only partially prevented by the addition of glucose to the system. This pattern is compatible with that of intermediate "primaquine sensitivity."

CASE 6.—A premature white infant of Scotch-Irish descent, whose birth weight was 2,098 gm. Pregnancy and delivery had been normal. Respirations were spontaneous. Jaundice was noted at 24 hours of age and persisted for three to four weeks. The infant was admitted to another hospital at the age of 18 days and was found to have anemia (hemoglobin, 7.1 gm. %) and reticulocytosis (15%). The patient was seen at that time by one of us (W. W. Z.). The liver edge was palpable, but the spleen was not felt. No serological incompatibility of the mother and child was demonstrated. The peripheral blood smear showed a considerable number of marked distorted erythrocytes as well as polychromasia and nucleated erythrocytes. After transfusions the hemoglobin rose to 12.0 gm. %, and the patient was sent home.

Course.—Two weeks later the hemoglobin had dropped to 7.8 gm. %, and the patient was admitted to Children's Hospital. The spleen was palpable at this time. The peripheral blood smear showed 5.0% distorted erythrocytes (Fig. 6, *a*). There were 2.4% reticulocytes. No Heinz bodies were seen. The direct Coombs test was negative and the indirect Coombs test of the mother's serum with the infant's cells was negative. The mother's type was O, Rh-positive (CDe), while that of the infant was O, Rh-negative (cde). The osmotic fragility was normal. Mechanical fragility was 5.7%. Urinalysis was normal, and the BUN was 10.5 mg. %. The liver spectrum was also normal. Red cell reduced glutathione and glucose-6-phosphate dehydrogenase were normal.

After further transfusion, the hemoglobin was maintained, and the erythrocyte morphology returned to normal. The infant subsequently showed a neurologic picture of cerebral palsy compatible with sequelae to bilirubin encephalopathy.

CASE 7.—A sibling of Patient 6, first seen by us at 18 days of age. Her birth weight was 2,892 gm. The labor and delivery had been normal. The mother had had a miscarriage at 6½ months in the 20-month interval after the birth of Patient 6. Three months prior to the delivery of Patient 7 the mother had received a sulfonamide because of a kidney infection, but this medication was discontinued after two days because of fever, chills, and a skin rash. Subsequently she was given tetracycline (Achromycin) for 10 days. There was no other history of exposure to drugs either in the mother or the infant. The infant was operated on at another hospital for omphalocele on the day of delivery. At 3 days of age the infant became jaundiced, and the bilirubin reached a peak of 14.6 mg. % on the seventh day. No serologic incompatibility between mother and child was demonstrated. The child was discharged from the hospital.

At the age of 17 days the infant was noted to be pale and was found to have a hemoglobin of 6.2 gm. %. On admission to Children's Hospital on the following day she appeared alert and active, but marked pallor was noted. The liver was palpable 2 cm. below the right costal margin and the tip of the spleen was felt 1 cm. below the left costal margin. A Grade II systolic murmur was heard over the precordium.

Laboratory Findings.—The hemoglobin was 4.9 gm. %, and there were 21.9% reticulocytes. The white blood count was 58,000/cu. mm. The peripheral blood smear showed marked polychromasia, nucleated erythrocytes, and some spherocytes; 33% of the erythrocytes were pyknocytes (Fig. 6, *b*). Heinz bodies were present in most of the erythrocytes except in pyknocytes on a smear stained with brilliant cresyl blue. The direct Coombs test was negative and the indirect Coombs test of the patient's serum with O, Rh-positive cells and O, Rh-negative cells was also negative. The infant's blood group was O, Rh-negative (cde), that of the mother O, Rh-positive (CDe). Bone marrow aspiration showed erythroid hyperplasia. Erythrocyte reduced glutathione was normal and the glucose-6-phosphate dehydrogenase was elevated (570 units). The latter finding was probably related to the reticulocytosis. Urinalysis was normal. Transaminase was 135. The bilirubin was 2.6 mg. % total and 0.25 mg. % direct. There was no growth on the blood culture.

Course.—Following two packed-cell transfusions, the hemoglobin was 8.0 gm. %, and shortly before discharge the patient was given another transfusion of 50 cc. of packed cells. The reticulocytosis remained marked (up to 25%) throughout the six days of her hospital stay. Subsequently her hemoglobin stabilized at 10.6 gm. %, and the peripheral blood film at 3 months of age showed that the erythrocyte morphology had returned to normal, and she appeared to be developing normally.

CASE 8.—A 23-day-old white female infant whose birth weight was 2,580 gm. The chief complaint was pallor and jaundice of one day's dura-

tion. The pregnancy and delivery had been normal. Respirations were spontaneous, and no jaundice was noted in the immediate neonatal period until the age of 22 days. At that time pallor as well as icterus of the skin and sclerae were noted. The liver was palpable 2-3 cm. below the right costal margin, and the tip of the spleen was felt.

Laboratory Findings.—Hemoglobin was 4.6 gm. %, and the reticulocyte count 15.7%. The white blood count was 50,000/cu. mm.; the differential showed 37 neutrophils, 58 lymphocytes, and 5 monocytes. The peripheral blood smear showed polychromasia and 16 nucleated erythrocytes per 100 white blood cells; 25.8% of the erythrocytes were pyknocytes. After supravital staining of the blood, no Heinz bodies were seen. The mother's blood type was Group A_1, Rh-positive (CDe) and the infant's was identical. The serum bilirubin level was 7.45 mg. % total with 0.2 mg. % direct reacting. The direct Coombs test of the mother's serum with the infant's cells and with Group O, Rh-positive and Rh-negative cells was negative. Urinalysis was normal, and the blood culture showed no growth.

Course.—After investigation the infant received two small packed cell transfusions, which raised the hemoglobin to 10 gm. %, and she was sent home. When seen three weeks later by the private physician the hemoglobin had dropped to 7 gm.; the reticulocyte count was 20%, and she was readmitted to the Children's Hospital of Michigan. On this admission (age 6 weeks) the direct Coombs test was again negative. The osmotic fragility of the erythrocytes was slightly decreased; erythrocyte mechanical fragility was normal. The hemoglobin electrophoresis revealed Type A hemoglobin, and there was 13.1% fetal hemoglobin (these studies were done after transfusion). Red cell reduced glutathione level and glucose-6-phosphate dehydrogenase were normal as were similar studies on the infant's parents. Repeat urinalysis was normal and the BUN was 12 mg. %. The liver spectrum was not abnormal, but the serum glutamic oxaloacetic transaminase level was 235 units.

The infant was again transfused twice with packed erythrocytes and discharged to the care of her private physician. Since the age of 2 months she has done well. There has been no recurrence of her hemolytic process and her hemoglobin has been maintained at 12 gm. %. She is now 8 months of age.

Comment

In 1949 Schwartz and Motto [1] described a special type of poikilocyte characterized by the presence of one or several spiny projections along its periphery. They termed this type of erythrocyte a "burr cell" and reported its occurrence in azotemia and occasionally in gastric carcinoma and bleeding peptic ulcer. They did not find such cells in the blood of 100 normal adults and stated that the presence of burr cells should always suggest renal involvement.

Dacie [2] in 1954 described essentially the same type of cell in patients suffering from rapidly progressive renal failure but in his description he stressed the features of contraction and distortion of the erythrocytes rather than the spiny projections. He also noted the occurrence of such cells in carcinomatosis and hepatic failure and stated that their appearance in some cases was accompanied by a hemolytic anemia. Aherne [10] in 1957 studied the relationship of burr cells to nitrogen retention and found that in general these cells do not appear in significant numbers until the blood urea nitrogen rises to levels above 175-200 mg. %.

In childhood, erythrocytes which seem to fit the description of burr cells have been observed by several authors in a syndrome first described by Gasser [11] in 1955 under the name uremic-hemolytic syndrome and characterized by the triad of severe renal disease, hemolytic anemia, and thrombocytopenia. Allison [12] reported on a group of infants who had this syndrome and illustrated and described the abnormal erythrocytes in detail as "contracted, distorted and deeply stained" erythrocytes. The same blood picture was subsequently observed by Shumway and Miller [13] in a 7-year-old child with a similar syndrome.

Erythrocytes which cannot be distinguished from burr cells according to the published descriptions and illustrations were also observed by Gasser [14] and later by Allison [12] in cases of severe toxic hemolytic anemia with marked Heinz body formation in premature infants who had received overdoses of vitamin K. Gasser termed the distorted cells "ruptured egg shell" forms and interpreted their shape as evidence of disintegration of cells damaged by toxins. In

his group of premature infants the appearance of such forms invariably followed the development of Heinz bodies in a large percentage of the erythrocytes. These phenomena occurred within a narrow age range, 1-3 weeks.

The fact that burr cells occur physiologically in the blood of full-term and premature infants, and the existence of a hemolytic anemia of young infants associated with substantial numbers of such cells in the absence of Heinz body formation and without evidence of drug ingestion or renal, hepatic, or other primary disease, seem to have escaped previous notice.

The morphologic identity of the distorted erythrocytes in the blood of the infants described above with the cells variously described as "burr cells" and contracted, distorted, and deeply stained erythrocytes, or ruptured egg-shell forms, is beyond doubt. The resemblance between such cells and those encountered in the toxic hemolytic anemia associated with naphthaline poisoning originally described in this laboratory [15] is at most superficial. The characteristic feature of the latter type of cell, also encountered in favism by Sansone et al.,[16] is the irregular loss of hemoglobin from the erythrocyte resulting in the development of a sharply delineated marginal area of pallor outlined faintly by the contour of the stroma. While the border between the hemoglobin-containing and the dehemoglobinized portion of the cell may be irregular and serrated, the contour of the cell as a whole is relatively smooth. The residual hemoglobin in such cells stains deeply and appears concentrated, but the spiny projections from the margin seen in "burr cells" are absent.

The distinction no longer rests on morphologic grounds alone, since it has been shown that the erythrocytes of patients susceptible to naphthaline poisoning, favism, and certain other toxic substances are deficient in glucose-6-phosphate dehydrogenase and manifest an instability of reduced glutathione in the red cells which is not prevented by glucose. In the patients studied by us the glucose-6-phosphate dehydrogenase was normal in five of six cases. In the sixth case (Patient 1) the patient was studied in this respect when she was 5 years of age and a so-called intermediate pattern was found. To date the development of toxic hemolytic anemias of the type encountered in primaquine reactors has been documented only in persons showing the complete enzymatic abnormality of the erythrocytes. It appears unlikely therefore that the finding of an intermediate pattern in this patient is more than coincidence, all the more because she had not been exposed to drugs at the time when pyknocytosis and hemolytic anemia were first observed. The absence of an abnormality in the glutathione mechanism of the other five patients speaks for itself and corroborates the assumption that there was no connection between this mechanism and the phenomenon of pyknocytosis in any of our cases.

A distinction between the distorted erythrocytes which form the subject of this paper and the bizarre erythrocytes described by Bassen and Kornzweig [17] and by Singer, Fisher, and Perlstein,[18] in patients with a celiac syndrome, atypical retinitis pigmentosa, and neurologic manifestations is not easily established. Singer et al.[18] coined the term "acanthrocytes" for the abnormal erythrocytes observed by them and considered such cells to be different from burr cells, although both have irregular spiny projections. These authors stressed the density of the cell body of the acanthrocyte as contrasted with that of the burr cell. However, from the descriptions and published illustrations as well as from our own observations, it appears that burr cells or irregularly contracted erythrocytes likewise have the characteristic deeply stained, dense-appearing bodies, and the evidence for a valid distinction on morphologic grounds alone between these cells and acanthrocytes is unconvincing.

There is, nevertheless, reason to consider acanthrocytosis a separate entity. Singer et al.[18] emphasized that in acanthrocytosis

the misshapen cells amount to 70%-80% of the total erythrocyte population. The highest number of misshapen cells in the cases observed by us was slightly over 50% in one case and less in all others. Whether this quantitative difference is in itself an adequate criterion is a moot question. However in the cases of Bassen and Kornzweig [17] and Singer et al.[18] there was evidence for a permanently expressed genetic defect. Their patients were of consanguineous Jewish parentage, and the deformity of the cells was a permanent feature and was not associated with an anemia. In our cases and in those associated with azotemia or observed in the course of toxic hemolytic anemia with Heinz body formation, distorted erythrocytes were not a majority of the red cell population and their presence was a transient phenomenon associated with a hemolytic anemia.

We propose the term "pyknocyte" for these cells because the density of the cell body appears to be a fundamental feature and the presence of spiny projections on the surface has already given rise to the term "acanthrocyte" for the red cells seen in another condition. The term "pyknocyte" is less unwieldy than other names already in the literature and is not prejudicial in terms of the pathogenesis of any syndrome associated with the presence of such cells. It appears that a minimal degree of pyknocytosis is physiologic in early infancy, a fact which may have significant implications in terms of the genesis of the distortion. We propose to designate the pathologic accentuation of this phenomenon associated with a hemolytic anemia, as described by us in 11 individual cases, infantile pyknocytosis.

As to the mechanism which produces these cells, the observations of their occurrence in azotemia and in hepatic disease, as well as in association with certain known toxic hemolytic anemias, suggests the effect of extracorpuscular factors acting on the red cells as proposed by Dacie.[2]

In the remarkable case of Shumway and Miller [13] the abnormal erythrocytes were observed in large numbers and the hemolytic anemia became marked whenever there appeared to be an exacerbation of the primary process especially after infection and were absent or virtually absent during the intervals. The authors were unable, however, to establish a correlation between pyknocytosis and nitrogen retention. Our observations concerning the gradual increase in pyknocytes in normal infants and especially in prematures in the absence of manifest hemolytic anemia, as well as the transient character of the pyknocytosis in the patients with hemolytic anemia, likewise suggest an extracorpuscular mechanism of transitory character. The apparent transformation of transfused donor erythrocytes in the case of Patient 1 tends to substantiate this assumption.

It was not possible to determine the nature of this mechanism but it appears that it is in some way linked to metabolic processes or changes characteristic of early infancy. Shumway and Miller, because of the association of pyknocytosis and hemolytic anemia with clinical evidence of acute infection in their case, were led to speculate that the underlying mechanism might be one of hypersensitivity. For infantile pyknocytosis such a mechanism on a priori grounds as well as because of lack of evidence, seems to us extremely unlikely. The possibility that the primary disturbance may reside in an alteration of hepatic function not detected by the usual liver function tests cannot be ruled out. The neonatal liver is especially vulnerable to a variety of insults connected with the transition from intrauterine to extrauterine life and is moreover known to be deficient in several enzyme systems. The observed range of values for serum glutamic-oxaloacetic transaminase in the blood of apparently normal newborn infants is higher than that of other age groups,[19] and may well denote functional liver damage which few infants may be able to escape. We consider the values of 257, 235, 135, and 110, at 20, 23, and 18 days, and 1½ months,

respectively, in four infants (Patients 10, 8, 7, and 6), as probably abnormal for this age and they may well provide the only clue to the possible role of hepatic dysfunction in the genesis of infantile pyknocytosis.

The assumption of some kind of extracorpuscular mechanism does not, of course, exclude factors intrinsic to the erythrocytes themselves. The existence of differences in enzyme activity and other chemical properties between newborn and adult erythrocytes is rapidly being documented, but with the means at our command we were not able to correlate the observed anomaly with such factors.

The existence of a genetically determined factor is strongly suggested, despite the transient character of the pyknocytosis, by the racial distribution of the patients and by the familial incidence documented in one family and strongly suggested by the history in another. The similar racial background of three of our patients (those with the earliest onset, Patients 1, 2, and 3), and the patients with acanthrocytosis described by Bassen and Kornzweig[17] and by Singer et al.[18] is of interest, as is the fact that in the severest case (Patient 1) the parents were consanguineous.

If a genetic factor plays a part in the development of infantile pyknocytosis, it should be clear that it may become manifest only under certain conditions which are at least in part age-determined. It is conceivable that the genetic predisposition which may lead to the development of pyknocytosis in early infancy, because of as yet unknown metabolic processes characteristic for this age, might become manifest in older persons under the impact of such environmental factors as frank renal or hepatic disease. The finding that in all newborn infants, and especially in those prematurely born, some degree of pyknocytosis exists greater than that found in adults, suggests, however, that the metabolic situation in the newborn may mimic to a slight extent such a genetic defect. Analogies to such a situation are already known; for example, the tendency for erythrocytes of newborns and primaquine reactors to form Heinz bodies on in vitro exposure to acetylphenylhydrazine.[20]

Summary and Conclusions

The regular occurrence of small numbers of distorted and contracted erythrocytes or burr cells in the blood of apparently normal full-term infants and especially in premature infants is described. The term "pyknocytes" is proposed for these erythrocytes. The percentages range from 0.3%-1.9% in full-term infants and 1.3%-5.6% in premature infants. In both groups the number of these cells increases with age up to at least 2-3 months.

Eleven cases of a hematologic entity are described which seem to be an accentuation of the physiologic presence of pyknocytes in early life and is characterized as an acute severe hemolytic anemia, in which up to 50% pyknocytes are found. The term infantile pyknocytosis is proposed for this entity. It is not associated with demonstrable renal or hepatic disease, ingestion of toxic substances, or as a rule, Heinz body formation. It is one of the conditions associated with neonatal hyperbilirubinemia. It is transient and responds to transfusion therapy. Its development appears to be age-determined but there is a strong probability that racial and genetic factors play a part.

5224 St. Antoine St. (2).

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Chondroectodermal Dysplasia (Ellis-van Creveld Syndrome)

Report of a Case and Review of the Literature

WILLIAM L. WALLS, M.D.; DONALD H. ALTMAN, M.D., and OLIVER P. WINSLOW, M.D., Miami, Fla.

Ellis and van Creveld [1] in 1940 described two patients who presented ectodermal dysplasia affecting the nails, teeth, and hair; polydactyly; chondrodysplasia, and congenital heart disease. Their report included a third patient, previously described by McIntosh [2] in 1933, who showed all of the congenital anomalies of the other two cases except congenital heart disease.

Since that time 24 additional cases have been reported in 16 papers.[3-18] Three other cases reported as examples of this syndrome by Keizer and Schilder,[19] Debre et al.,[20] and Gallagher et al.[21] are lacking in one or more of the minimal requirements and therefore have not been included in this review. It is the purpose of this paper, in addition to presenting another case, to discuss briefly the diagnosis, the variability of the manifestations, and the hereditary factors in this syndrome. The increase in the number of cases reported in the past five years would seem to indicate that chondroectodermal dysplasia is not as rare as was once believed.

The diagnosis can be made on inspection of the patient, even immediately after birth. There is shortening of both upper and lower extremities, especially below the knees and elbows, with short stubby hands, with polydactyly and sometimes syndactyly. There is hypoplasia of the nails and sometimes hair. The teeth, if erupted, are usually dysplastic.

The diagnosis can be confirmed by the radiological appearance of the skeleton. These findings have been well described by Caffey.[5] The tubular bones in the extremities are shortened and thick. This shortening of the bones of the arms and legs becomes progressively increased from the trunk to the distal phalanges. Dwarfism is almost always due to shortening of the legs. Bilateral manual polydactylism is almost always present. The usual number of digits is six per hand with the extra digit characteristically seen on the ulnar side of the hand. Polydactylism in the feet is the exception rather than the rule. Syndactylism and synmetacarpalism are common. The carpal bones may also be fused, especially the capitate and hamate. Delayed ossification in the primary centers and accelerated ossification of the secondary centers of the metacarpals and phalanges are usually present.

The proximal ends of the ulnae and distal ends of the radii are usually larger than normal. The distal ends of the ulnae and the proximal ends of the radii are too small. Occasionally, there is a discrepancy in length between the radii and ulnae leading to compensatory dislocation of the radial heads.

The proximal ends of the tibial shafts are widened and sharpened into low peaks with short medial slopes and relatively long lateral slopes. The medial slopes are capped by thin hypoplastic ossification centers in the proximal epiphyseal cartilages. This deformity is pathognomonic of the Ellis-van Creveld syndrome, and accounts for the classic genu valgum deformity. The patellae are usually normal. Skull films may demonstrate delayed and abnormal dentition.

Submitted for publication Jan. 26, 1959.

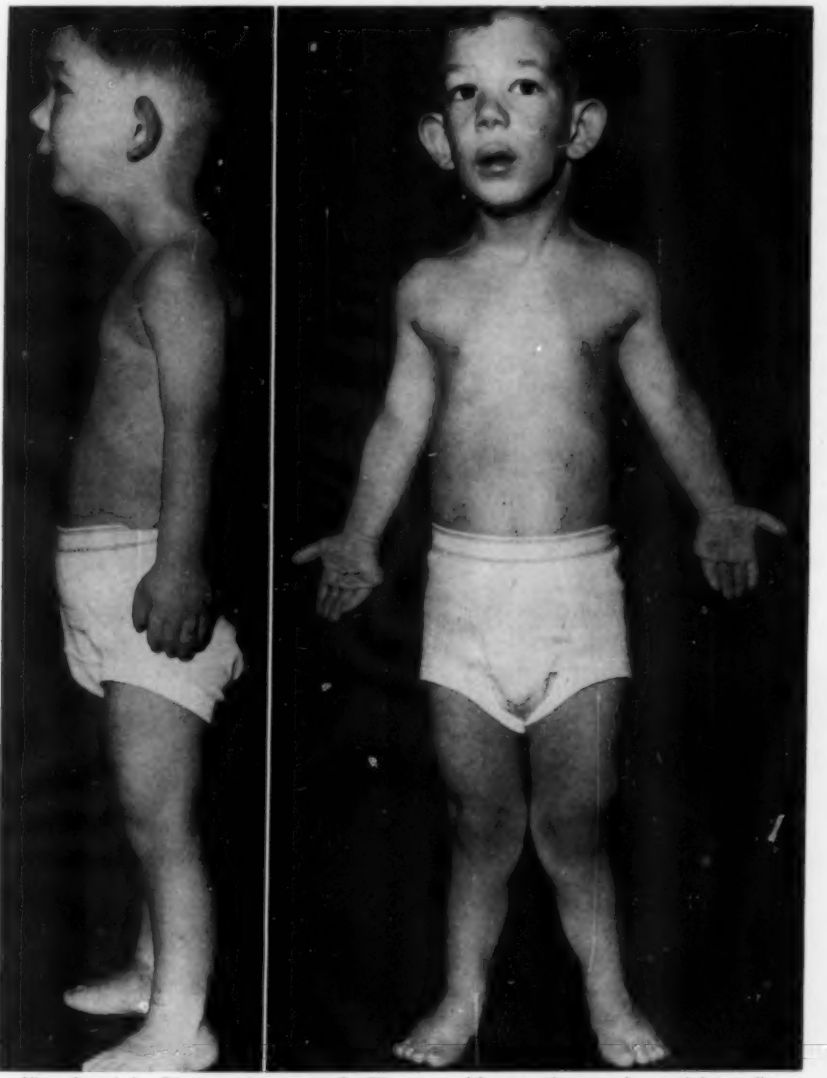
Department of Radiology, Variety Children's Hospital, Miami, Fla.

Report of Case

A white boy was born on Oct. 25, 1952, after an uneventful pregnancy and uncomplicated vaginal delivery. The mother, 30 years old at the time of delivery, is of Scotch-Irish descent. The father, 34 years of age at the time of the birth, is of Italian descent. An exhaustive study revealed no evidence of any congenital defect in the family of either parent. There was no consanguinity. The mother has had no other pregnancies.

The child weighed 6 lb. 1 oz. (2,750 gm.) at birth and showed normal responses. Examination just after birth revealed an extra digit on the ulnar side of each hand. The nails were quite hypoplastic and irregular. The extremities showed progressive distalward shortening.

The child has progressed well up to the present time. He has always been active and has good coordination. He has above-average intelligence. The extra digits were removed at the age of 18



Figs. 1 and 2.—Photographs at age 5. The extremities are short, owing mainly to disproportionate shortening distal to the elbows and knees. The head is normal in size, and the trunk is normal in length. The hair is normal.

Fig. 3.—Photograph of teeth. The lower central incisors are absent. The premolars are capped. The remaining teeth are irregular in size and shape.

months. The patient also had a hypospadias, which was repaired. The teeth were slightly delayed in eruption and at first were thought to be normal, but very soon became carious and shell-like with use. The premolars had to be capped.

Physical examination at this time (November, 1958) reveals a height of 39 in. and a weight of 31 lb. These figures are both below the normal range for a child of this age. The hair is normal both in quality and distribution. Examination of the teeth shows the lower incisors absent (Fig. 3). The premolars are capped. The remaining teeth are somewhat irregular in size and shape. Examination of the heart is unremarkable except for a soft Grade I to II blowing systolic murmur at the apex and at the pulmonic region. The abdomen is negative. The genitalia are normal except for a moderate degree of hypospadias with corrected chordee.

Fig. 4.—Photograph of hands. The ulnar side of each hand shows a residual defect resulting from surgical amputation of the sixth digit. The hands are short and wide. The digits are shortened, especially distally. All of the nails are small, deformed, and set back on the finger tips.

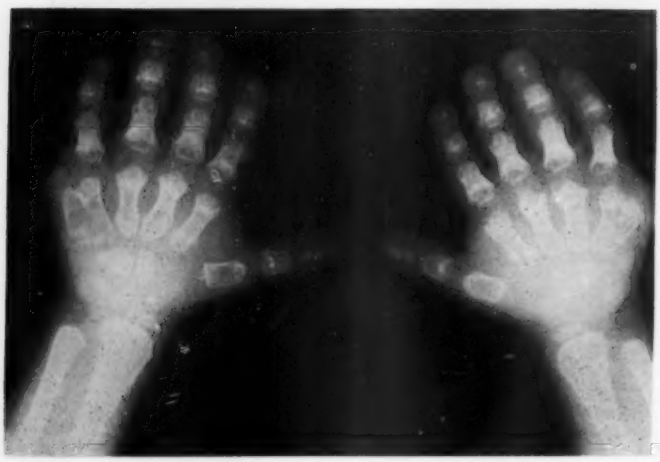


Fig. 5.—Roentgenogram of hands. The fifth and sixth metacarpals are fused side to side. The 6th digit has been removed, but the residual soft-tissue defect remains. The proximal phalanges are short and thick with cupped bases, opposite which there are relatively large ossification centers in the proximal epiphyseal cartilages. The middle phalanges show similar but more pronounced changes. However, in the distal phalanges the primary centers are hypoplastic while the secondary centers are barely visible. The maturation of the proximal and middle phalanges is accelerated. Note individual carpal bones, without a carpal mass.

The extremities show progressive distal shortening. The trunk comparatively appears to be elongated. The hands are flat and broad, and there is a bilateral protuberance at the site of the amputation of the extra digit. The nails are small, fine and immature and do not extend to the finger tips. The fingers are broad, with most pronounced shortening distally (Fig. 4). A genu valgum is is present.

The roentgenographic studies of the chest show some stubbing of the lower ribs. The heart is normal in size and contour. All of the bones of the extremities are shortened, the shortening being more pronounced distally. The hands show a residual defect on the ulnar side at the site of previous amputation (Fig. 5). The fifth and sixth metacarpals are fused side to side. The proximal phalanges are short and thick with cupped bases, opposite which there are relatively large ossification centers. The tibiae and fibulae are shortened (Fig. 6). The proximal ends of the tibial shafts are widened and sharpened into low peaks with shorter medial slopes and longer lateral slopes. The ossification center of the proximal tibial epiphysis is hypoplastic and triangularly shaped and caps the medial slope of the metaphysis.

Fig. 6.—Roentgenogram of lower extremities. Both the tibiae and fibulae are shortened, with relatively greater shortening of the fibulae. The proximal ends of the tibial shafts are widened and sharpened into low peaks with shorter medial slopes and longer lateral slopes. The medial slopes are capped by a hypoplastic, triangularly shaped ossification center in the epiphyseal cartilages.

All of the cases reviewed demonstrated ectodermal dysplasia, polydactyly, and chondrodysplasia. Only 15, or about one-half of the cases, demonstrated cardiac abnormalities. Seven of the patients died in the neonatal period. In all of these cases the congenital heart lesion was a prominent feature and it was felt to be the cause of death. One case reported by Caffey subsequently died at the age of 14 months from heart failure. Two of the cases autopsied showed triloculation of the heart with a single auricle. Another heart was two-chambered and the remaining three had large septal defects. The cardiac lesion in most of the living cases was diagnosed as a septal defect. The prognosis in this syndrome probably depends on the severity of the cardiac malformation, if one is present. It should be noted, however, that congenital heart disease need not be present in order to make a diagnosis of chondroectodermal dysplasia.

The ectodermal dysplasia is manifested generally by defects of the teeth, nails, and hair. The teeth are retarded in their development and are imperfectly formed, variously shaped, and irregularly spaced. The nails are usually small, deformed, and often very friable. These may have distal thickening, longitudinal ridges, or may be entirely absent. The hair may be normal. A few cases demonstrated partial alopecia. Epispadias and hypospadias have also been reported. Several of the cases demonstrated obliteration of the sulcus between the upper lip and gum. In three of the cases the mid-portion of the upper lip was underdeveloped, giving the appearance of a pseudoharelip. A true harelip was reported in one case. The sweat mechanism of all of the patients was grossly normal.

The mentality in the surviving patients has usually been normal. Four of the cases are retarded and one is an imbecile.

McIntosh's patient is now a university graduate.

Many additional or coexisting malformations have been reported. Eye manifestations included strabismus, bilateral colobomata of the iris, and congenital cataracts. Several patients demonstrated severe genu valgum deformities, and a few had club feet. Deformities of the pelvic bones, especially in the acetabulum, were described. Three of the cases had pedal polydactylism. Hepatosplenomegaly was present in six instances, although the exact relationship of this finding to the underlying pathology was not clear. One case demonstrated hypergammaglobulinemia.

It may be seen from the accompanying Table that no sexual predilection exists. Of the cases reported, 14 were female and 14 were male. All of the cases have occurred in members of the Caucasian race except one, a Negro, reported by Smith and Hand.[17] No ethnic predisposition exists. Eleven different ethnic groups are represented, namely, Dutch, English, French, German, Italian, Irish, Jewish, Negro, Polish, Swiss, and Turkish.

In all of the reported cases, the entire known ancestry has been unaffected, except in one instance in which a grandfather had an extra digit on each hand. This syndrome has been reported in siblings of three different families. Metrakos and Fraser[9] reported chondroectodermal dysplasia occurring in a 5-year-old boy and his 3-year-old sister; and in dizygotic twin brothers 18 years of age. The third instance, reported by Mitchell and Waddell,[18] occurred in

Summary of Reported Cases of Ellis-van Creveld Syndrome

Case	Author & Year	Age	Sex	Parental Consanguinity	Congenital Heart Disease	Intelligence	Remarks
1	McIntosh (1933)	19 yr.	F	Yes	No	University Grad.	Reported subsequently by Ellis, van Creveld, & Caffey
2	Ellis & van Creveld (1940)	20 mo.	F	Yes	I. V. septal defect	Normal	
3	Ellis & van Creveld (1940)	4 yr.	M	No	I. V. septal defect	Normal	
4	Weiler (1951)	2 yr.	F	No	I. A. septal defect	Retarded	
5	Gatto (1951)	15 yr.	F	Yes	Septal defect	Retarded	
6	Caffey (1952)	3 ½ yr.	F	No	No	Normal	
7	Caffey (1952)	14 mo.	F	No	I. V. septal defect	Deceased	
8	Debre et al. (1952)	14 ½ yr.	F	No	Yes (Type ?)	Normal	
9	Neiman et al. (1953)	6 ½ mo.	M	Yes	Yes (Type ?)	—	
10	Midulla (1954)	11 yr.	F	Yes	No	Slightly retarded	
11	Metrakos & Fraser (1954)	14 yr.	M	No	No	Normal	
12	Metrakos & Fraser (1954)	5 ½ yr.	M	No	No	Normal	
13	Metrakos & Fraser (1954)	3 yr.	F	No	No	Normal	Sibling of Case 12
14	Metrakos & Fraser (1954)	18 yr.	M	No	No	Below average	
15	Metrakos & Fraser (1954)	18 yr.	M	No	No	Imbecile	Dizygotic twin of Case 14
16	MacGregor (1954)	7 yr.	M	—	No	Normal	
17	Chauss (1955)	29 wk.	F	No	Trilocular (Single auricle)	Deceased	
18	Weiss & Crosett (1955)	9 mo.	M	No	No	Normal	
19	Turner (1956)	Neon.*	M	No	Trilocular (Single auricle)	Deceased	
20	Akoun & Bagard (1956)	Neon.	F	No	Trilocular (Single auricle)	Deceased	
21	Weyers (1956)	Neon.	F	Yes	Septal defect	Deceased	
22	Weyers (1956)	1 yr.	M	Yes	No	Apparently Normal	
23	Uehlinger (1957)	Neon.	M	No	I. V. septal defect	Deceased	
24	Smith & Hand (1958)	Neon.	M	No	Septal defect	Deceased	Negro
25	Smith & Hand (1958)	Neon.	M	No	Cor biloculare	Deceased	
26	Mitchell & Waddell (1958)	3 ½ yr.	F	Yes	I. A. septal defect	Normal	
27	Mitchell & Waddell (1958)	5 yr.	F	Yes	No	Normal	Sibling of Case 26
28	Present (1958)	6 yr.	M	No	No	Normal	

* Neonatal.

sisters, aged 5 and 3 years. Another sibling of this family, a girl who died at the age of 8 days, was said to have been blue from birth and had extra digits on both hands.

A complete sibling analysis in the present series is not possible because of incomplete information in some of the cases reported. Also the number of families involved is probably too small for adequate statistical evaluation. However, it would appear that the number of actual recurrences is quite compatible with that which would be expected on the basis of simple recessive inheritance.

Parental consanguinity was present in 9 of the 25 families reported, whereas in the general population it is present in about 1 out of 100 families. It is assumed, therefore, that the frequency of consanguinity in the present study is not due to chance. The finding of an increased rate of consanguinity in the parents of children with a rare disease is evidence for recessive inheritance of that disease.[22]

The authors agree with Mitchell and Waddell that the present name of this syndrome, chondroectodermal dysplasia, is a misnomer. This term describes the defects of bone and of ectodermal tissue while giving no indication of the involvement of other mesodermal derivatives. It is suggested, therefore, that a more appropriate and comprehensive name would be mesoectodermal dysplasia.

Summary

An additional case of Ellis-van Creveld syndrome is reported, and the literature is completely reviewed.

Ectodermal dysplasia, polydactyly, and chondrodysplasia must be present to make the diagnosis. Congenital heart disease may or may not be present.

The diagnosis is easily made by examining the patient and is confirmed by radiological examination.

An autosomal recessive mode of inheritance is strongly suggested.

Mesoectodermal dysplasia is proposed as a more descriptive name for this syndrome.

Department of Radiology, Variety Children's Hospital (Dr. Altman).

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Case Reports

Lamellar Exfoliation of the Newborn, or Ichthyosis Congenita

NADINE G. SMITH, M.D., and NORTHROP BEACH, M.D., Minneapolis

A baby who was born with a collodion-like membrane over the entire body has recently been under our observation. We used the term "lamellar exfoliation of the newborn" introduced by Grass and Török [1] but observed the baby for two years before establishing a final diagnosis. The actual significance of this term is not clear, nor is its use universally accepted. Shelmire Jr.[2] recently reviewed the literature and found 15 cases of this entity. He proposed preservation of the term lamellar exfoliation of the newborn as descriptive of a distinct entity and suggested that the frequent association of this defect with ichthyosis is but another example of multiple congenital ectodermal defects. He noted, however, that even in the mildest cases there was usually residual dryness and desquamation of the skin. In reviewing the literature on this subject,[3-5] we found only one instance in which the skin was described as being perfectly normal after several years.[6] In this case the membrane present at birth covered only the dorsum of the hands and feet. Falk [7] preferred to simplify classification by retaining Riecke's original grouping of the three types of ichthyosis congenita. In this classification, lamellar exfoliation of the newborn would be included under that group of cases of ichthyosis congenita in which infants are born with a collodion-like sheath and may die during early weeks of life. Different classifications of ichthyosis congenita appear in other articles and texts but serve only to confuse the reader further.[8-10]

We believe that the case to be reported supports the theory that lamellar exfoliation of the newborn is a form of ichthyosis congenita and is rarely followed by a skin free from ichthyosis. This case brings the number of recorded cases of this entity to 24.

Report of Case

A white male infant was delivered at term in his local hospital on March 13, 1957. This was the mother's third normal pregnancy. The family history was noncontributory.

The membranes ruptured spontaneously 24 hours before delivery. Labor was of eight hours' duration and uncomplicated. At birth the baby appeared slightly cyanotic. The skin was described as extremely thin, red, and generally swollen. The baby was admitted to our hospital five hours after delivery.

On physical examination, the baby was found to be normally developed. The weight was 2,450 gm. The skin was erythematous, edematous, and wrinkled. There was generalized superficial desquamation, most noticeable on the abdomen and legs. There were no bullae, pustules, or fissures. The feet and hands were moderately cyanotic. The face was especially swollen. There was minimal eversion of the upper eyelids. The external auditory canals were edematous. There was a moderate eclabium with a slight surrounding desquamation. Other than the skin, physical examination showed no abnormality, except that the testicles were not palpable in the scrotum.

Laboratory data were as follows: hemoglobin, 20.7 gm.; leukocytes, 11,700 per cubic millimeter, with a differential count of 57% polymorphonuclear cells, 41% lymphocytes, and 2% eosinophils. There was a trace of albumin in the urine. A culture of exudate from the eyes was reported as showing no growth.

Treatment consisted of aqueous penicillin administered intramuscularly; phenobarbital sodium,

Submitted for publication Feb. 4, 1959.

Instructor in the Department of Dermatology, University of Minnesota School of Medicine (Dr. Smith).

Fig. 1.—The infant at 3 days of age, showing the ectropion, eclabium, and collodion-like membrane.

given as necessary for twitching; Burow's solution wet packs applied to the intertriginous areas, and 3% salicylic acid ointment applied to the scalp and extremities.

The baby was afebrile throughout his hospital stay. After 24 hours the external layers of the skin on the trunk began to peel in large sheets, much like collodion, and the underlying skin appeared normal. It was then that the diagnosis of lamellar exfoliation of the newborn was suggested. On March 16, the collodion-like membrane began to peel from the face and scalp, and the ectropion and eclabium had decreased. On March 18, the membrane was still peeling in sheets but the baby was

Fig. 2.—The infant at 16 days of age. There is a fine desquamation present over the trunk and extremities.

Fig. 3.—The boy's legs at 14 months of age. There is dryness and desquamation, most marked over the feet.

noticeably improved. On March 21, at the age of 8 days, the major peeling was almost complete, except for a very fine desquamation over most of the body. The eyes were normal. The weight was 2,950 gm. The baby was discharged on March 21, 1957.

One month later there was minimal scaling on the back and upper chest. The scalp was considerably more scaly than the rest of the skin. The extremities and trunk were dry.

On Aug. 6, 1957, the skin appeared normal except for mild ichthyosis, most marked on the hands and feet. There was some scaling on the soles and in the scalp. The face was quite normal. Because of anhidrosis, he occasionally has had an elevated temperature on hot summer days. The boy is now 2 years of age and has shown no further change.

Therapy

A few therapeutic suggestions are worthy of note. Williamson [11] called attention to the fact that the diaper area in a case of congenital ichthyosis remained smooth as long as diapers were worn. This observation may have led to the use of sodium chloride in ointment form and in the bath. In 10% concentration in an ointment base, sodium chloride has been found very effective in ichthyosis.[12] It is preferable to long-term use of salicylic acid ointments which may result in toxicity when used over large areas. Recently very dramatic reports have appeared concerning the use of massive doses of vitamin B_{12} given intramuscularly every day in conjunction with 1 gm. of vitamin C taken orally.[13] Presumably vitamin B_{12} is capable of influencing epithelial growth and keratinization. Clinically there has been noted marginal detachment of scales as early as five days after the institution of therapy. In five cases so treated there were no side-effects from the drug. One severe case was entirely free of ichthyosis after three months of treatment.

Summary

A case of lamellar exfoliation of the newborn is presented which, after two years, continues to show ichthyosis. Because of the residual ichthyosis in this and in most cases, it is probably wise to consider this disease as a relatively benign variant of ichthyosis congenita rather than as a distinct entity. Two reportedly helpful therapeutic suggestions are offered.

1021 Medical Arts Building (2).

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Disseminated Histoplasmosis Treated with Amphotericin B

RUTH M. HEYN, M.D., and SAMUEL T. GIAMMONA, M.D., Ann Arbor, Mich.

Disseminated histoplasmosis occurring in infancy is a disease which usually terminates fatally. Only nine cases of survival in infants have been reported. Various forms of therapy, including supportive measures and the use of such drugs as ethyl vanillate and the diamidine group of compounds, have been used in the treatment of this disease.

It is the purpose of this paper to present the first case of disseminated histoplasmosis in an infant treated successfully with amphotericin B and the 10th reported case to survive with or without treatment. This infant, at the time of this writing, is living and well one year after his acute illness.

Report of Case

At the age of 3 months, this infant boy developed the typical clinical features of disseminated histoplasmosis with an insidious onset of fever, cough, anorexia, weight loss, and progressive hepatosplenomegaly. As his spleen enlarged his blood counts showed progressive effects of hypersplenism with the development of pancytopenia. He was hospitalized elsewhere during the ensuing two months for study and, because of a positive histoplasmin skin test, bone marrow was taken for culture and, in addition, a biopsy of spleen and liver was obtained. Histoplasma capsulatum organisms were seen in the spleen aspirate, and cultures from the marrow subsequently grew the organism. He was sent to University Hospital for further care at the age of 5 months.

This infant was born in a small community near Flint, Mich., where he had lived since his birth. This area has not been known to be endemic for histoplasmosis. The county health department has studied the home area and has not been able to find a source of histoplasmosis. Histoplasmin skin tests and chest films on the family revealed a positive skin test on only the father.

At the time of admission physical examination showed a poorly developed, poorly nourished infant, who was pale and appeared both acutely and chronically ill. He was listless and unresponsive to his surroundings. His temperature was 104 F. The eyes, ears, nose, and throat appeared normal. The lungs were clear, with a respiratory rate of 30. The heart was not enlarged, and no murmurs were heard. The abdomen was markedly protuberant. A firm liver was palpated 5 cm. below the costal margin, and the spleen was felt at the iliac crest. A poorly healed laparotomy scar was noted in the left upper quadrant. There was generalized poor muscle tone, and he was unable to support his head. The reflexes were active and equal bilaterally. There was no lymphadenopathy present except for small inguinal nodes on the left.

During his early hospitalization his counts dropped to a low of 6.8 gm. % hemoglobin; 1,850 WBC, and 43,000 platelets. Liver function tests revealed an increased total globulin of 3.04 gm. % and a cephalin flocculation of 4+. Four separate histoplasmin skin tests were done at varying times during his hospitalization and all were negative. Two tuberculin skin tests, using 1:4,000 O. T. and 1:1,000 O. T., were negative. Cultures on Sabouraud's media were obtained from gastric washings, bone marrow, and blood. Bone marrow films revealed an erythroid hyperplasia and the presence of a very small number of Histoplasma capsulatum organisms found primarily in large macrophage cells. Subsequently the bone marrow grew Histoplasma capsulata. The blood and gastric washings remained negative. Complement fixation tests obtained for cryptococcosis and blastomycosis were negative, while complement fixation tests for histoplasmosis were positive.

In the hospital he continued to have temperatures of 104 F daily, remained anorexic, and showed progressive weight loss. On his 10th hospital day he was started on amphotericin B intravenously. This was tolerated well and continued for a total of 21 days, with a final total dose of 120 mg. He became afebrile after four days of treatment and remained so throughout the rest of his hospital stay. On the 10th day of therapy his appetite began to improve and he began to gain weight. Another bone marrow aspiration was done after three weeks of therapy and was found to be normal.

Submitted for publication Dec. 15, 1958.

Department of Pediatrics and Communicable Diseases, University of Michigan Medical School. Present address of Dr. Giammona, 2125 Plainfield Ave. N.E., Grand Rapids, Michigan.

TABLE 1.—*Cultures and Complement Fixation Tests Before and After Therapy*

	Date	Marrow Culture	Spleen Culture	Complement Fixation Antigen 1	Complement Fixation Antigen 2
Before therapy	11/ 7/57	Positive	Positive		
	11/12/57			1:64	1:128
	11/14/57	Positive			
After therapy	12/17/57	Negative		1:256	1:128
	2/12/58			1:32	1:64
	9/10/58			No titer	No titer

TABLE 2.—*Reported Cases of Survival from Disseminated Histoplasmosis in Infancy*

Author	Cases	Treatment
Bunnell and Furcolow [1]	5 mo. male	Supportive care only
	20 mo. female	Irradiation of spleen and splenectomy
Blumberg et al. [2]	2 mo. female	Supportive care only
Klingberg [3]	19 mo. female	Penicillin and streptomycin
Christie et al. [4]	8 mo. male	Ethyl vanillate
	5 mo. male	
	5 yr. male	
	1 yr. male	
	9 mo. female	

No organisms were seen and no growth has occurred from this aspirate. A gradual improvement in liver function has occurred. A summary of his cultures and complement fixation tests is given in Table 1.

During his therapy he became increasingly responsive and would smile and show awareness of his surroundings. By the time of discharge he was able to support his head. His spleen at that time was palpable at the level of the umbilicus, and his liver was 2 cm. below the costal margin. He was discharged to his home 38 days after admission, approximately 3 months after the onset of his illness. He has been seen several times since discharge and has grown and developed normally. His last visit was at the age of 15 months. There were no abnormal physical findings, and he appeared to be a happy normal baby. Subsequent histoplasmin skin test and a chest film at 18 months of age are both negative.

Comment

Although it is generally accepted that the histoplasmin skin test is negative in the active stages of disseminated disease, in this instance it was the positive test which suggested the diagnosis initially. When skin tests were repeated on four subsequent occasions during his active disease, negative tests were obtained. The period required for the growth of the organisms in culture in this patient was five weeks for those taken in the local hospital and two weeks for those in our hospital. Because of this extended period before diagnosis could be assured on a culture basis, it was helpful to identify the organisms in marrow films and tissue material. Of additional help in this period were the positive serologic tests for histoplasmosis. Either a rising or a falling titer, as well as a single high titer, can be considered presumptive evidence of some stage of disease.

There are nine reported cases of infants who have recovered from disseminated histoplasmosis. These cases are tabulated in Table 2. In the review on histoplasmosis by Peterson and Christie [5] in 1955, the only drugs which were found to have any therapeutic effectiveness in the disseminated disease were ethyl vanillate and quinacrine (Atabrine). The latter has been used in mice only. The use of ethyl vanillate has been difficult from the standpoint of its administration, the toxic effects, and the duration of therapy required.

Amphotericin A and B are obtained from a newly found species of Streptomyces isolated from a soil sample obtained from South America.[6-8] The active material is a yellow crystalline substance whose chemical structure is not known. There is very little absorption of the drug from the gastrointestinal tract in both dogs and man, necessitating its intravenous administration. A continuous intravenous drip must be employed in order to prevent adverse reactions. Cardiac dysfunction and convulsions have been reported following rapid infusion of the drug both in experimental animals and humans.[9,10] A single daily dose of drug is, therefore, administered slowly over a six- to eight-hour period, using a freshly prepared solution each day. The action of the material is thought to be fungicidal. The presently available material is a water-soluble salt of amphotericin B in sterile dry

powder form. The B salt is used rather than the A because of the greater effectiveness of the former against histoplasmosis, demonstrated in mice. It is recommended that the initial daily dose be 0.5 mg. per kilogram of body weight. If toxic signs do not ensue in 24 to 41 hours, this should be increased to 1.0 or 1.5 mg. per kilogram per day. The reported toxic symptoms in patients include fever, nausea, vomiting, anorexia, and phlebitis at the site of injection. Increased blood urea nitrogen without evidence of renal impairment has been seen when large doses are used. The infant in this report showed no adverse effects attributable to the drug. His drug was given in continuous intravenous drip, the site being changed every three to seven days. Since the ideal duration of amphotericin administration has not yet been determined, treatment was discontinued after 21 days in this patient because of the marked improvement observed.

Amphotericin B has shown fungicidal activity against many infections in animals [11-15] and its clinical use has been reported for blastomycosis, cryptococcosis, coccidioidomycosis, and histoplasmosis.[16-21] Rubin et al.[19] were the first to report the use of amphotericin B in human infection with histoplasmosis. They treated a man with severe pulmonary histoplasmosis with oral drug initially, then after 10 days gave the drug intravenously. With the change of administration to the intravenous route, there was an immediate and continued improvement in his clinical course.

Only two groups have reported the use of amphotericin B in disseminated disease thus far. Lehan et al.[20] included six patients with disseminated histoplasmosis in a large series of patients receiving amphotericin B for various fungus diseases. Only four of these received intravenous medication, and, of these, two received drug for only a few days prior to death and two adults are well several months after completing therapy. Utz et al.[17] have reported the use of amphotericin B in three patients with disseminated disease. One of these was a 6-month-old infant with far-advanced disease, who died after 20 days of treatment, the drug having been administered intravenously the last 15 days. Of the two adults, one died while on the oral drug and the other responded after 90 days of the intravenous drug and had been well for four months at the time of publication.

The usual clinical course of disseminated histoplasmosis is a progressive downhill one followed by death in three to eight weeks. Because this infant showed a deteriorating course and amphotericin B was available, its use was felt to be indicated.

Summary

The course of a 5-month-old infant with disseminated histoplasmosis who was treated with a new fungicidal antibiotic, amphotericin B, is reported.

The favorable outcome of this infant one year after therapy and the negative cultures obtained three weeks after treatment was begun are encouraging. Because of the reported toxic effects of amphotericin B, one should carefully observe the patient for any reactions during its use. However, it would appear further clinical trial is justified in the treatment of severe disseminated histoplasmosis.

We wish to thank Dr. E. Richard Harrell from the Department of Dermatology and Syphilology for his advice in the care of this patient.

Amphotericin B is available as "Fungizone."

University Hospital.

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Abstracts from Current Literature

Acta pædiatrica, Stockholm

Abstracted by William W. Cleveland, M.D.

47, No. 3 (May) 1958

* Aetiology of Non-Diphtheritic Croup: I. Bacteriologic and Serologic Investigation. Lennart Philipson.—p. 265.

47, No. 4 (July) 1958

* On the Amount of Gastric Contents in the Normal and the Asphyxiated Newborn Infant. Björn Westin.—p. 354

47, No. 5 (Sept.) 1958

* Separate Renal Function Studies in Predominantly Unilateral Hydronephrosis. Rolf Zetterström, Nils Olof Ericsson, and Jan Winberg.—p. 540.

Aetiology of Non-Diphtheritic Croup: I. Bacteriologic and Serologic Investigation.—The term "croup," as used in this report, refers to an acute illness in children characterized by "metallic, hoarse cough, breathing difficulties, and/or inspiratory stridor," and includes various conditions, such as supraglottic laryngitis, subglottic laryngitis, and acute laryngotracheobronchitis."

Bacteriologic and serologic studies were made in 269 admittances of patients with nondiphtheritic croup in an effort to further clarify the nature of the infectious agents involved. The clinical features of these illnesses, such as age and sex of the patients, fever, elevation of WBC, eosinophilia, and sedimentation rate were also analyzed. By far the commonest organism present in the respiratory tract of these children was Staphylococcus aureus pyogenes, which was present in 51.3% at admission and 61.8% at discharge. In only one case was a rise of antibody to staphylococci noted, and the prevalence of this organism both on admission and discharge was interpreted to indicate that it had little etiologic significance.

Pneumococci, β-hemolytic streptococci, and Hemophilus Influenzae were isolated in only a very small number of cases, and hence were felt not to have major significance as etiologic agents. The authors conclude from their studies that nondiphtheritic croup is most likely of viral etiology in the majority of cases if it is an infectious disease at all.

Comment: This study serves to reinforce the prevailing impression that croup is rarely due to bacteriologic agents. The isolation of viral agents suspected of being pathogenic has been reported in individual cases, and the author intimates that he has isolated such agents in this disease and will report this work in further communications.

On the Amount of Gastric Contents in the Normal and the Asphyxiated Newborn Infant.—Previous reports have presented data to support the proposition that aspiration of the gastric contents of the newborn delivered by Caesarean section lessens the incidence of asphyxia and reduces the mortality in such infants.

Questioning the validity of this conclusion, the author studied the quantity of gastric fluid present in several groups of infants by immediate aspiration of gastric contents with a catheter and 5 ml. syringe. The mean amounts of fluid present in the stomachs of infants in the various groups are as follows:

1.—229 normal deliveries (no signs of asphyxia prior to or after delivery) 3.2±0.2 ml.

2.—6 low-forceps deliveries (no signs of asphyxia) 2.4±1.3 ml.

3.—12 spontaneously delivered asphyxiated infants 4.8±1.1 ml., and

4.—15 asphyxiated infants delivered by mid-high or low forceps 3.1±2.0 ml.

The differences between the various groups are considered to be insignificant. The author reaches the following conclusion from these data: "If the unchanged volume depended on the fact that part of it had been aspirated by the lungs prior to the delivery, as in a more rapid passage to the bowels, the respiratory distress of the newborn does not seem to be improved by the suction of a small amount of gastric fluid."

Comment: Following the evaluation of the practice of gastric aspiration of newborn infants delivered by Caesarean section, and its recommendation by Gellis et al. in 1949, this procedure has been widely employed. Other controlled studies have indicated its value in

* These articles are abstracted in this issue.

reducing the incidence of asphyxia. The data and conclusions in this report would appear to question the value of this practice, but the conditions of this study make its reliability questionable. The infants studied here were not delivered by Caesarean section, and it is in this group—and particularly offspring of diabetics—that Gellis found a marked increase in gastric contents; the values found by him for babies delivered via the pelvic route agree fairly well with the values reported here. It should also be noted that the chief value of this practice is in prevention of delayed bouts of asphyxia, not that present at birth. Gellis has also emphasized the value of mechanical suction in increasing the efficiency of the aspiration.

Separate Renal Function Studies in Predominantly Unilateral Hydronephrosis.—Two patients with hydronephrosis were studied. In both, the disease was marked on one side and comparatively mild on the other. During periods when a pyelostomy tube was draining the severely diseased kidney, advantage was taken of this situation to study the separate function of the two kidneys by obtaining simultaneous specimens from the pyelostomy tube and bladder.

Studies of acid-base regulation revealed in the diseased kidney of both patients a defective base reabsorbtion in the usual metabolic state, as well as in response to administration of an acid load. Similarly there was marked disparity of the kidneys in the ability to conserve water by concentration of urine. This response was demonstrated both as a result of thirsting and the failure of response to Pitressin. The results of these tests are discussed in relation to current knowledge of tubular function, and it is concluded that there is evidence of disturbance of both proximal and distal tubular function in the severely hydronephrotic kidney.

Comment: This study is of considerable interest as regards the disturbed physiology of renal disease, and makes ingenious use of a not uncommon clinical situation. One is reminded of the work of Connor et al. (*Bull. Johns Hopkins Hosp.* 100:241, 1957) in which bilateral ureteral catherization, with study of urine flow and sodium concentrations simultaneously from the two sides were done. In adults this approach yielded valuable information regarding the contribution of unilateral renal ischemia to hypertension. There are few data of this sort available from studies of children, and the test is technically more difficult in the small patient.

American Heart Journal, St. Louis

Abstracted by F. Kathryn Edwards, M.D.

57, No. 1 (Jan.) 1959

* Anomalous Left Coronary Artery Arising from the Pulmonary Artery. William J. Kuzman, Anton S. Yuskis, and David B. Carmichael.—p. 36.

Systolic Clicks: A Clinical, Phonocardiographic, and Hemodynamic Evaluation. Kareem Minhas and Benjamin M. Gasul.—p. 49.

Tricuspid Stenosis in Association with Right Ventricular Hypertrophy and the Coexistence of Right-Sided Endocardial Fibroelastosis. Zahira Hafez Abdin and Fatma Hafez Abdin.—p. 98.

An Embryologic Explanation for the Corrected Transposition of the Great Vessels: Additional Description of the Main Anatomic Features of This Malformation and Its Varieties. Maria V. de la Cruz, Guillermo Anselmi, Fernando Cisneros, Michel Reinhold, Bolivar Portillo, and Jorge Espino-Vela.—p. 104.

57, No. 2 (Feb.) 1959

Hypoplasia of the Aorta: Report of a Case. Kalevi Pyorala, Per-Erik Heidel, and Pentti I. Halonen.—p. 289.

Isolated Congenital Pulmonic Valvular Regurgitation. B. L. Lendrum and A. B. Shaffer.—p. 298.

57, No. 3 (March) 1959

Importance of the Unipolar Leads in the Diagnosis of Dextrocardias, Levocardias, Dextropositions, and Dextrorotations. Bolivar Portillo, Guillermo Anselmi, Demetrio Sodi-Pallares, and Gustavo A. Medrano.—p. 396.

Extrathoracic Ectopia Cordis: Report of Cases and Review of Literature. Robert F. Milhouse and Howard A. Joos.—p. 470.

Anomalous Left Coronary Artery Arising from the Pulmonary Artery.—The authors report three cases of anomalous left coronary artery arising from the pulmonary artery which were seen in a five-month period—all three cases were diagnosed during life. The authors think the diagnosis can be made during life if attention is directod to the clinical symptoms, physical findings, the electrocardiogram, and radiologic findings.

The typical clinical features are as follows: 1. An apparently normal infant, between the ages of 2 and 4 months of age, develops respiratory wheezing, tachypnea, and difficulty in feeding, with frequent regurgitation of feedings. 2. Attacks of colicky pain, pallor, profuse sweating, tachycardia, and peripheral cyanosis occur in association with feedings or immediately after feedings.

The physical examination usually shows no murmurs. The heart may be enlarged and the infant may be tachypneic.

The electrocardiogram is important, for it characteristically shows left ventricular hypertrophy associated with "coronary type" T wave changes. Deep Q waves are often present in Leads T, aVL, and the left precordial leads. These changes are those commonly associated with extensive anterolateral ischemic changes in an adult.

The prognosis is extremely poor in infants; however, several authors have reported long-term survival. Treatment consists of surgical anastomosis of the anomalous vessel to the aorta or one of its branches during cardiac bypass. Surgical therapy was attempted in only one of the patients reported. All three infants were critically ill and died in the first few months of life.

The disease is most frequently confused with vascular ring or aspiration of a foreign body, or recurrent lower respiratory infection.

American Journal of Pathology, Ann Arbor, Mich.

Abstracted by Jay Bernstein, M.D.

35, No. 2 (March-April) 1959

Cytoplasmic Inclusions Resembling Guarnieri Bodies, and Other Phenomena Induced by Mutants of the Virus of Fowlpox. E. W. Goodpasture.—p. 213.

* The Suppression of Lesions and the Development of Immunity by Means of Antihyaluronidase in Vaccinia and Fibroma Infections. John M. Pearce and Donald Weeks.—p. 233.

* Localization of Colloidal Substances in Vascular Endothelium: A Mechanism of Tissue Damage: II. Experimental Serum Sickness with Acute Glomerulonephritis Induced Passively in Mice by Antigen-Antibody Complexes in Antigen Excess. Robert T. McCluskey and Baruj Benacerraf.—p. 275.

Experimental Production of Congenital Malformations in Rats by Salicylate Poisoning. Josef Warkany and Eva Takacs.—p. 315.

A Pathologic Human Embryo. Charles R. Green.—p. 333.

Experimental Dietary Siderosis. Theodore Gillman, M. Hathorn, and P. A. S. Canham.—p. 349.

Histogenesis of Branchial Cysts: A Report of 468 Cases. Surindar N. Bhaskar and Joseph L. Bernier.—p. 407.

Study of Functional Activity of Adrenocortical Cells with Electron Microscopy. Charles T. Ashworth, George J. Race, and Hilton H. Mollenhauer.—p. 425.

The Suppression of Lesions and the Development of Immunity by Means of Antihyaluronidase in Vaccinia and Fibroma Infections.—Following observations on experimental infection with the Shope fibroma virus, in which hyaluronidase increased the size of the lesion produced by intradermal injection of the infectious agent and antihyaluronidase tended to suppress the lesions, similar studies were carried out with vaccinia. It was demonstrated that the simultaneous injection of vaccinia virus and antihyaluronidase resulted in a relatively mild disease in rabbits, without diminishing either the rabbits' immunity to subsequent inoculation or the level of their circulating antibodies.

Localization of Colloidal Substances in Vascular Endothelium: A Mechanism of Tissue Damage: II. Experimental Serum Sickness with Acute Glomerulonephritis Induced Passively in Mice by Antigen-Antibody Complexes in Antigen Excess.—The repeated injection into mice of soluble antigen-antibody complexes—rabbit antiovalbumin or antibovine serum albumin antiserum with an excess of ovalbumin or bovine serum albumin, respectively—resulted in the production of acute glomerulonephritis in all the animals surviving to the end of the experiment, acute endocarditis in a third of the animals, and acute arteritis in a few of the animals. Several animals died from anaphylactic shock following the first injection. The injection of human γ-globulin and histamine produced only slight glomerulitis.

Circulation, New York

Abstracted by Anthony C. Nolke, M.D.

17, No. 6 (June) 1958

* Observations on the Mechanism of Atrial Gallop Rhythm. James J. Leonard, Arnold M. Weissler, and James V. Warren.—p. 1007.

* Radiologic Aspects of Operable Heart Disease: VI. Changes Following Surgical Closure of P. D. A. Philip Strauss, Herbert L. Abrams, and Saul Robinson.—p. 1047.

* Anomalous Coronary Arteries with Special Reference to Arteriovenous-like Communications. Jesse E. Edwards.—p. 1001.

Observations on the Mechanism of Atrial Gallop Rhythm.—Gallop rhythm is said to be present when an audible diastolic sound is added to the two normal heart tones. It is a low-pitched sound occurring after atrial systole, but before the subsequent ventricular contraction. This sound is frequently heard in patients with hypertensive cardiovascular disease,

myocardial infarction, and in the presence of atrioventricular conduction disturbances (heart block, complete or partial).

Eighteen patients were studied with hypertensive cardiovascular disease. The systolic pressures were 200 mm. Hg or over, the diastolic pressure over 110 mm. Hg in all. All patients had x-ray or EKG evidence of left ventricular hypertrophy. Pneumatic cuffs 6 in. wide were placed around all extremities to pool the blood in the extremities, with resultant lowering of intracardiac pressures. All sound tracings were recorded on a Sanborn twin beam photographic instrument.

Atrial gallop sounds may occur (1) when atrioventricular conduction is prolonged or (2) when altered pressure volume relationships result in an earlier atrial sound. Delay in onset of the first heart sound may enhance the tendency toward gallop production.

Radiologic Aspects of Operable Heart Disease: VI. Changes Following Surgical Closure of P. D. A.—The preoperative radiologic findings in patent ductus arteriosus have been carefully studied and recorded. An effort has been made to determine the magnitude, character and rapidity of the changes observed, as well as the relationship of past operative change to complicating cardiovascular lesions. This study adds to the existing studies in the literature.

There were 165 consecutive cases of surgically corrected patent ductus arteriosus; 71 of these patients had sufficient preoperative and postoperative films available for analysis. The ages of the patients ranged from 6 months to 15 years. Most cases were followed clinically and radiographically for one to five years.

Several conclusive observations were made:

The cardiothoracic ratio was greater than 0.50 in 52 patients, and less than 0.50 in 19. In 50 of the 52 patients with a cardiothoracic ratio of greater than 0.50, there was a significant decrease apparent postoperatively. Among the 19 with a cardiothoracic ratio of less than 0.50, 15 showed a significant diminution.

All children under 10 years of age with an uncomplicated patent ductus demonstrated a decrease in the cardiothoracic ratio postoperatively.

There was enlargement of the left ventricle in 54 of 71 patients; 45 showing diminution in size postoperatively.

Left atrial enlargement was present in 50 of 71 cases, 40 of whom showed return to normal size postoperatively.

The right ventricle was suggestedly enlarged in 50 cases, with diminution to normal in 42.

Right atrial enlargement was difficult to assess and usually occurred with right ventricular hypertrophy.

The pulmonary thoracic ratio seemed larger than normal in 60% of cases; in 65 cases the pulmonary artery segment was felt to be unduly prominent. The central (hilar) pulmonary arteries were increased in size in 56 cases, as were the peripheral pulmonary arteries.

The aortic convexity sign was of more significance in the older age groups, usually over 10 years of age, when the knob was more prominent.

Changes in the pulmonary vascularity occurs rapidly and can be significant after a few hours; two months postoperatively the vessels may appear virtually normal, and beyond six months little alteration can be expected. The heart size changes occur at a slower rate; by two months the major changes in heart size occur.

Pulmonary hypertension need not represent a poor prognostic sign and may not indicate increased pulmonary resistance. Markedly elevated pressure and the left-to-right shunt is small; this reflects increased resistance and a poor prognosis.

If after six months no significant changes have occurred in the size, a complicating lesion should be expected and sought.

The incidence of conotruncal abnormalities was higher in patients whose mothers had German measles early in their pregnancies.

Anomalous Coronary Arteries with Special Reference to Arteriovenous-like Communications.—Previous classifications of anomalies of the coronary arteries have been on an anatomic basis. The author attempts to classify such anomalies on a functional basis as most of them have in common features of arteriovenous-like communications.

Anomalies of the coronary artery system fall into three major groups: (*a*) those of minor significance where the arteries make no unusual communication with the cardiac chambers, coronary veins, or pulmonary trunk; (*b*) coronary anomalies secondary to the

effects of certain primary cardiac malformations, as aortic or pulmonic atresia; and (c) major anomalies of the coronary arteries which make the patient susceptible to cardiac failure, myocardial ischemia, and bacterial endarteritis. These have communication with the right side of the circulation, yielding a left-to-right shunt and anomalous communication of the coronary arterial system with the left atrium or ventricle, causing a functional disturbance similar to that of aortic insufficiency.

In each condition there is tortuosity and dilatation of the portion of the arterial system which is part of the abnormal communication; a feature common to all arteries proximal to abnormal arteriovenous communications.

The theory offered by the author is that the blood flows from the anomalous coronary artery into the pulmonary trunk. These vessels usually anastomosed over the cardiac wall with the normally arising arteries and there is a run-off of blood flow from the normally arising vessel into the anomalous one, and thence into the pulmonary trunk.

Journal of the American Medical Association, Chicago

Abstracted by Don M. Hosier, M.D.

169, No. 1 (Jan. 3) 1959

Carcinoma of the Thyroid in Children After X-Ray Therapy in Early Childhood. D. R. Rooney and R. W. Powell.—p. 1.

* Therapy of Acute Attacks of Asthma in Infants and Children. J. P. McGovern.—p. 20.

Therapy of Acute Attacks of Asthma in Infants and Children.—The author first lists factors due to age that are of prime importance in influencing the therapeutic approach to the treatment of asthma in infants and children. The treatment of acute attacks of asthma is also divided arbitrarily into (1) early mild to moderate attack, and (2) more prolonged, severe attack (status asthmaticus).

At the first sign of prodrome of asthma the parents are instructed to give the child mild and properly balanced medication to effect bronchodilation and sedation. The author recommends ephedrine 7.5 mg. and secobarbital 15 mg. per teaspoonful in a palatable suspension. This may be given as necessary at four-hour intervals to abort an asthmatic attack. If a sudden severe attack is encountered, then aqueous epinephrine, 1:1,000 should be given immediately in appropriate doses (0.1-0.4 cc.). Hydration is also of utmost importance.

In the treatment of the severer attack or of status asthmaticus, epinephrine both in aqueous solution and in oil should be administered. If bacterial infection is present, the child should receive adequate treatment with sulfonamides or a broad-spectrum antibiotic. The author warns against the use of penicillin in an allergic child.

Only after the aforementioned treatment fails to block an attack, and there is no infection present or it is "covered" by antibiotic therapy, is steroid therapy advocated. The author outlines his method of steroid therapy for these children. Should all these measures fail, the child is then hospitalized for further treatment.

The statement is made that "needless to say, if a child is having uncontrolled polycyclic attacks of asthma, he should be evaluated by a competent allergist."

Medizinische Klinik, Munich

Abstracted by Samuel Amberg, M.D.

53, No. 46 (Nov. 14) 1958

* The Symptomatology of the Psychomotor Attack Syndrome in Children. R. Garsche.—p. 1972

53, No. 47 (Nov. 21) 1958

* Oxyruis Granulomas. L. Stark.—p. 2017.

53, No. 48 (Nov. 28) 1958

* The Occult Purulent Mastoiditis of Infants. A. Jonasch.—p. 2058.

53, No. 50 (Dec. 12) 1958

The Parenteral Pednisolone Treatment of Acute Diseases in Infancy and Childhood. H. D. Linden.—p. 2153.

54, No. 1 (Jan. 2) 1959

The Icterus Problem. F. Thoenes.—p. 1.

54, No. 2 (Jan. 9) 1959

Staphylococci Infections in a Pediatric Clinic During a Temporary Change to a Single Antibiotic. G. Linzenmeier.—p. 47.

The Symptomatology of the Psychomotor Attack Syndrome in Children.—The manifestations of psychomotor epilepsy during childhood are discussed. The diagnosis is more

difficult than in the adult because the symptoms often simulate reaction types which may occur in children without epilepsy, and so are less strikingly abnormal. The electroencephalogram taken between attacks in most cases indicates an attack disease but in some cases it may be constantly normal. The focal changes in the temporal lobes regarded as typical in adults are often absent, particularly in younger children. The incidence of psychomotor attacks in children is estimated at about 30%, while the association with grand mal is less frequent than in adults. It is recommended that the paper be consulted for detail.

Oxyuris Granulomas.—The possibility of an appendicitis oxyurica is postulated. This is to be differentiated from the appendicopathia ex oxyure of Aschoff. Various localizations of oxyuris granulomas are given.

The Occult Purulent Mastoiditis of Infants.—Unexplained disturbances of development and nutrition, toricosis, and septic manifestations arouse the suspicion of an occult mastoiditis. The various means of otologic examination are discussed, including rhinoscopy and roentgen examination. With improved technique of roentgen examination, it is stated that in 60% to 80% of cases a correct diagnosis can be made. Indications for puncture of the antrum or antrotomy and of conservative treatment are discussed. It is emphasized that occult mastoiditis is not without symptoms but is poor in symptoms, indicating rather the shorter or longer latent periods during which antibiotic treatment is not recommended.

The Parenteral Prednisolone Treatment of Acute Diseases in Infancy and Childhood.—The intravenous administration of prednisolone sodium succinate is recommended as emergency treatment in cases of excessive reactions of inflammatory, toxic, and allergic origin. It was given in a dosage of 2-4 mg/kg. every 12 hours for two to three days, depending mainly on the severity of the disease. Often it was possible to substitute I. M. injections as early as the second day. In addition, a broad-spectrum antibiotic was given, as well as other treatment. Of the original 43 cases, some illustrative examples are described.

The Icterus Problem.—A review of the icterus problem in infants and children is presented.

Staphylococci Infections in a Pediatric Clinic During a Temporary Change to a Single Antibiotic.—The study was made in a children's hospital of 180 beds, a home for children with 50 beds, and a nursing school with 50-60 pupils. For a period of 16 months erythromycin only was used for all responding infections, particularly those due to staphylococci. Patients and personnel were constantly subjected to bacteriological control with determination of the resistance of the organisms to various antibiotics, sulfonamides, and their lysotopy (by test phages). Therapeutically, this temporary change proved successful, although previously penicillin-resistant staphylococci remained resistant.

New England Journal of Medicine

Abstracted by Demetrius G. Traggis, M.D.

259, No. 16 (Oct. 16) 1958

* Surgical Correction of Defective Absorption of Vitamin B_{12} in a Child. W. C. Quinby Jr. and J. J. McGovern.—p. 755.

The Free Achilles Reflex in Hypothyroidism and Hyperthyroidism. J. D. Lawson.—p. 761.

A Comparison of Bacterial Counts of the Urine Obtained by Needle Aspiration of the Bladder, Catheterization and Midstream-Voided Methods. O. T. Monzon, E. M. Ory, H. L. Dobson, E. Carter, and E. M. Yow.—p. 764.

Effect of Aluminum Hydroxide on the Intestinal Absorption of Chloramphenicol. T. Takasu, L. Bosco, B. J. Clark, and H. W. Marraro, p. 767.

Menstruation and Systemic Disease. J. Rogers.—p. 770.

Mesenteric Adenitis Due to Pasteurella Pseudo-Tuberculosis in Young People. W. Knapp.—p. 776.

Chlorpromazine-Type Cholangitis: Report of a Case Occurring After the Administration of Prochlorperazine. R. C. Mechanic and L. Meyers.—p. 778.

259, No. 17 (Oct. 23) 1958

Idiopathic Hypercalcuria. P. H. Henneman, P. H. Benedict, A. P. Forbes, and H. R. Dudley.—p. 802.

Bedside Measurement of Alveolar Carbon Dioxide Tension. H. A. Ravin and M. Stein.—p. 811.

Some Biochemical Aspects of Fibrogenesis and Wound Healing. D. S. Jackson.—p. 814.

* Current Status of Steroid Therapy in Rheumatic Disorders. J. S. Stillman.—p. 820.

259, No. 24 (Dec. 11) 1958

Observations on Antibiotics in the Treatment of Hepatic Coma and on Factors Contributing to Prognosis. J. M. Stormont, J. E. Mackie, and C. S. Davidson.—p. 1145.

Production of Impending Hepatic Coma by Chlorothiazide and Its Prevention by Antibiotics. J. E. Mackie, J. M. Stormont, R. M. Hollister, and C. S. Davidson.—p. 1151.
Ammonia Intoxication Treated by Hemodialysis. J. E. Kiley, J. C. Pender, H. F. Welch, and C. S. Welch.—p. 1156.
Malignant Cells in Peripheral Blood. J. C. Pruitt, A. W. Hilberg, and R. F. Kaiser.—p. 1161.
Anemia and the Spleen. A. G. Motulsky, F. Casserd, E. R. Giblett, G. O. Brown Jr., and C. A. Finch.—p. 1164.
Current Concepts in Therapy. p. 1172.

259, No. 25 (Dec. 18) 1958

° Physiologic Abnormalities of Salicylate Intoxication. W. E. Segar and M. A. Holliday.—p. 1191.
Bacteriology of the Bedside Carafe. C. W. Walter, A. D. Rubenstein, R. B. Kundsin, and M. A. Shilkret.—p. 1198.
Hemagglutination in Viral Hepatitis. W. P. Havens Jr.—p. 1202.
Shall We Count the Living or the Dead? M. C. Sheps.—p. 1210.
Anemia and the Spleen. A. G. Motulsky, F. Casserd, E. Giblett, G. O. Broun Jr., and C. A. Finch.—p. 1215.
Asian Influenza—Retrospect and Prospect. p. 1229.

259, No. 26 (Dec. 25) 1958

Familial Occurrence of Congenital Heart Disease: Report of Three Families and Review of the Literature. R. A. Carleton, W. H. Abelmann, and E. W. Hancock.—p. 1237.
Cerebral Vasospasm. J. L. Pool.—p. 1259.

Surgical Correction of Defective Absorption of Vitamin B_{12} in a Child.—The authors report a case of megaloblastic anemia secondary to a malfunctioning segment of bowel. At birth ileal atresia was present, which was excised, and an anastomosis was made from jejunum to cecum. For the next few months a short transit time from mouth to anus led to a slow weight gain, and there was a tendency to anemia and hypoproteinemia. At 4 years of age she still showed slow weight gain and hypochromic anemia. Further studies showed dilated loops of bowel which on reexploration were found to be dilated segments of jejunum proximal to anastomosis. The anastomosis was resected and remade but the dilated loops were left in place. At 5½ years of age she was again readmitted. She had continued to have poor weight gain and now presented with ankle edema, abdominal distention, melena, diarrhea, mild cardiac failure, a reddened, smooth tongue, and retarded mental and physical growth. Her anemia was found to be megaloblastic and responded very well to vitamin B_{12} intramuscularly. Her abdominal symptoms continued. A third operation was performed, and this time the dilated loops just proximal to the anastomosis were removed along with 4 cm. of colon. It should be noted that the lumen of the anastomosis had been adequate. Three ulcers were found in the removed segment of the ileum. Since this the child has improved in all respects. Peripheral blood and bone marrow studies along with the response to vitamin B_{12} proved the diagnosis of megaloblastic anemia. Co^{60}-labeled vitamin B_{12} was given and practically all recovered in her stools with no absorption. Free HCl was found. Her gastric juice, when incubated with Co^{60}-labeled vitamin B_{12}, showed normal absorption of the B_{12} in a patient with pernicious anemia (thus showing the presence of intrinsic factor). Two weeks after the operation (and 12 days of chloramphenicol and erythromycin) the absorption of Co^{60}-labeled vitamin B_{12} was 30%, and six weeks after cessation of antibiotics it was 49% in spite of the same rapid transit time of food as before surgery, thus implying that the dilated segments of bowel or their contents had been responsible for the poor absorption rather than the rapid transit time of food. The authors refer to 25 cases of the association of megaloblastic anemia with intestinal lesions. Either a blind loop or dilated bowel proximal to a stricture has been present in all cases. Megaloblastic anemia has been produced in dogs and rats by creating a blind loop in such a way that peristalsis constantly fills it. This anemia responds better to folic acid than to B_{12}. In some of the laboratory animals the anemia does not appear if the loop does not contain bacteria. Also it has been shown in some cases in humans with this syndrome that treatment with some of the broad spectrum antibiotics seems to increase the absorption of vitamin B_{12}. Noticeably, however, neomycin does not have this effect. Several authors have suggested that bacteria either bind vitamin B_{12} or produce a substance that interferes with the synthesis of antianemia principle. This problem, however, has not been solved.

Current Status of Steroid Therapy in Rheumatic Disorders.—The author first mentions some general principles of the use of cortisone and its derivatives. They may be used for replacement therapy or to block ACTH stimulation of the adrenal gland. Other uses are based on their anti-inflammatory, antiallergic, antitoxic, and regulatory properties. In the regulatory properties, it generally involves the mesenchyme and lymphoid tissue. Unde-

sirable effects of cortisone have been fluid retention, peptic ulcer, emotional disturbances, facial rounding, acne, and hypertrichosis. The problem of withdrawal was discussed. Abrupt withdrawal usually leads to a prompt exacerbation of the disease. He points out that injections of ACTH, given at the time that the steroids are being withdrawn, may increase the endogenous supply of cortisone. This in turn will also help to decrease the production of normal ACTH from the pituitary, thus leaving the patient with a gland that is not being stimulated. This suppression of the gland, particularly if it was prolonged, may last for many months, leaving the patient vulnerable to the stress of infection, surgery, and trauma. The author also points out that since these drugs do not cure most of the diseases, and, since symptoms often return when they are withdrawn and are particularly troublesome to the patient at that time, then starting the patient on the drug commits him to the use of cortisone for a very long period of time. The symptom complex of chronic hypercortisonism has recently been recognized. It occurs chiefly in rheumatoid arthritis and may also occur in systemic lupus erythematosus and scleroderma. It is associated with prolonged mild overdosage of the hormones. It is characterized by easy tiring, muscular, and joint aching, and emotional instability. In particular, depressed periods alternate with periods of marked overactivity. Objective changes in joints and muscles are very slight compared to the marked subjective symptoms. In some of these patients with chronic hypercortisonism, signs and symptoms suggesting systemic lupus erythematosus have developed. In a few others, lesions, similar to polyarteritis nodosa, have developed in patients with rheumatoid arthritis, usually during or shortly after the withdrawal of hormonal treatment. Chronic hypercortisonism should be treated by the withdrawal of the hormone. This must be done very slowly and the decrements usually have to be very small. The author mentions the use of local injections of cortisone such as in joints. He also discusses some modifications of cortisone, pointing out that the newer products have avoided the difficulties with sodium and water retention and potassium loss, but as yet are unproved as far as the other side-effects of cortisone are concerned. The author then goes on to discuss the use of steroids in various rheumatic disorders. In general, he feels that they should be used only in severe and unremitting disease in order to try to give the patient a reasonably active life. Under these circumstances one has to accept the disadvantages of the treatment. In most cases of rheumatoid arthritis aspirin appears to be the treatment of choice. Such factors as severe constitutional reactions and iritis are probably indications for steroid therapy. The author also points out the possibility of severe flare-up of psoriasis in patients who are being treated with steroids for rheumatoid arthritis. In rheumatic fever the author feels that the main indication for steroids is in those patients who have carditis and who have not responded promptly to large doses of salicylates. He points out that the drug should be given early and in large dosages in order to try to suppress the manifestations of the disease. Steroids appear to be of no benefit in patients with osteoarthritis, although there is some evidence to suggest that local injections in an involved joint may be helpful. Steroids have been found to suppress the manifestations of an acute attack of gout. Massive doses of cortisone up to a 1,000 mg. or more per day, may produce rather marked improvement in patients with systemic lupus erythematosus in acute crisis. There is little evidence that these drugs are helpful in scleroderma. In dermatomyositis there is evidence to suggest that the steroids markedly reduced inflammation and occasionally produced prolonged remissions. In polyarteritis nodosa the steroids have occasionally proved life saving.

Comment: The author's statements about the dangers of steroid therapy bear repeating. Hypercortisonism, in its chronic form, has been seen in children as well as in adults. The other dangers of cortisone therapy are well known. The fact that most of the diseases for which the steroids are used are not curable by the steroids mean that one should use the steroids only in a life threatening situation or in a situation in which the patient is threatened by severe and prolonged disability.

Physiologic Abnormalities of Salicylate Intoxication.—The authors report on the physiologic abnormalities in salicylate poisoning. Forty-nine children, all less than 6 years of age, form the basis of the report. Five died and all five were under 2 years of age. Of interest is that a history of ingestion was obtained in only 43 and only 11 had taken it themselves. The other 32 were a result of "misguided therapeutic efforts of the parents, often under the advice of a physician." Of the 49 children, 44 had fever on admission, 21 being over 104 F and 13 from 105-108 F. The five deaths occurred in the 105-108 F group. In discussing the hyperpyrexia the authors pointed out the following: Salicylate increases total heat pro-

duction, the locus of action probably being in skeletal muscle; it also, by action on the central nervous system, increases the normal mechanism of the loss of heat by evaporation of water from skin and lungs; in the presence of dehydration the normal mechanisms cannot function, and hyperthermia therefore develops. Carbohydrate metabolism is severely deranged by salicylates. Of 14 children in whom blood sugar levels were measured, 4 had fasting levels about 200 mg/100 ml. Also the conjugation products of salicylate will produce a positive reducing test in the urine (to Benedict's solution). The presence of coma, elevated blood sugar, and positive reducing substance in the urine, all of which may be seen in salicylate intoxication, may make the differentiation between diabetic coma and salicylate intoxication difficult. Four effects of salicylates on carbohydrate metabolism have been noted (mostly in studies on animals). They are as follows: 1. An increase in glucose demand or accelerated peripheral utilization of glucose. Salicylates will ameliorate diabetes in the experimental animal; this is the only effect that might tend to lower blood sugar. 2. Probable increase in the production of adrenocortical steroids (a stress phenomenon). 3. In animals they have been shown to increase the absorption of glucose from the GI tract. 4. They interfere with enzymes of the aerobic carbohydrate cycle leading to the failure of metabolizing pyruvate. Nos. 2, 3, and 4 lead to an increase of blood sugar. Twenty-seven of thirty children showed positive ketone bodies in the urine. Although sick children frequently show this because of starvation and depletion of hepatic and muscle glycogen, yet the blocking of carbohydrate metabolism by salicylates leads to ketosis in itself. In 19 cases in which pH was measured, it was found low in all 19. The authors point out that the first change that takes place is a respiratory alkalosis which may possibly lead to tetany, especially with injudicious use of alkali too early. However, none of their children were apparently seen in this stage. Metabolic acidosis was found to be a serious complication of salicylate intoxication. The initial hyperventilation leads to a decreased renal bicarbonate absorption and increased renal excretion of sodium and potassium bicarbonate in order to compensate for the loss of CO_2 in the lungs. Thus the patient starts out with a diminished buffer capacity. The acidosis results from derangement of carbohydrate metabolism leading to (1) accumulation of lactic and pyruvic acids and (2) to excess of ketone bodies because of the mobilization of fat for energy. Also salicylate itself is an acid. Starvation also plays a part. The fluid and electrolyte losses were discussed. Factors contributing to losses were hyperventilation and sweating, the frequent occurrence of vomiting and diarrhea, and initially the increased urine volume necessary to excrete the increased solute load. Because the marked insensible loss is without electrolytes and the large sweat loss is hypotonic, then either adequate water intake or adequate volume of urine is necessary to prevent the increase of solute in body fluids. In 25 cases in which serum sodium was determined values over 150 mEq/l were found in 5. In six of the eight children with convulsions hypernatremia was present (in the seventh sodium was normal and in the eighth it was low). Of six children whose temperature was over 105 F, sodium was elevated in three. Salicylate blood levels varied from 18 to 81 mg/100 ml. In the five deaths, salicylate levels were 45, 42, 81, 60, and greater than 60. Concerning treatment the authors feel that external cooling with cool water or even alcohol and adequate intravenous fluids are the essentials to correct therapy. Measures of serum electrolytes and pH will be helpful in determining the type of fluids to be given. Attempts to lessen the hyperventilation by the use of barbiturates or narcotics are contraindicated. Oxygen, which might depress respiration, should not be used unless necessary. Supportive measures such as vitamin K and C should be used.

Comment: This is an excellent article on salicylate intoxication. In the treatment of this condition the authors do not feel that alkali therapy is necessary. Certainly in the stage of respiratory alkalosis it is contraindicated. Several articles in the literature, however, suggest that the excretion of salicylate is increased when alkali is given. One other method of therapy should be kept in mind and that is exchange transfusion. This has been found to be of value.

Pediatrics, Springfield, Ill.
Abstracted by William W. Cleveland, M.D.

22, No. 3 (Sept.) 1958

* Cloaca with Non-Adrenal Female Pseudohermaphrodism. William K. Sieber and Robert Klein.—p. 472.

22, No. 4 (Oct.) 1958

* Acute Poisoning Associated with Inhalation of Mercury Vapor (Report of Four Cases).—p. 675.

22, No. 5 (Nov.) 1958

* The Treatment of Allergy with Extract of Toxicodendron Quercifolia: A Controlled Series. Sheldon H. Kamin, Leo Nastasi, William Westlin, and Allen H. Kline.—p. 887.

22, No. 6 (Dec.) 1958

* Development of Prematurely Born Children. Margaret Dann, S. Z. Levine, and Elisabeth V. New.—p. 1037.
Duodenal-Motility Patterns. G. J. Barbero et al.—p. 1054.
Metachromatic Leuko-Encephalopathy. R. F. Hain et al.—p. 1064.
Treatment of Tuberculous Pleural Effusions. M. H. D. Smith et al.—p. 1074.
Eventration of the Diaphragm. H. C. Bishop et al.—p. 1088.
Alterations in Blood of Fetuses of Diabetic Mothers. I. H. Kaiser et al.—p. 1097.
Transaminase Activity in Muscular Dystrophy. E. G. Murphy et al.—p. 1110.
Physiologic Hyperbilirubinemia of Premature Infants. G. H. Holman.—p. 1115.
Metabolic Studies of Infants Fed Intermediate Amounts of Protein. S. J. Fomon et al.—p. 1134.
Electroencephalographic Studies in Poliomyelitis. H. J. Grossman et al.—p. 1148.
Infantile Spasms. I. N. L. Low et al.—p. 1153.
Infantile Spasms. II. N. L. Low.—p. 1165.
Thallium Poisoning. P. H. Chamberlain et al.—p. 1170.
Splenic-Gonadal Fusion. J. R. Sommer.—p. 1183.
Public Health-Annual Summary of Vital Statistics.—p. 1189.
Renal Tuberculosis. J. K. Lattimer et al.—p. 1193.

Cloaca with Non-Adrenal Female Pseudohermaphrodism.—In a brief report, two cases are described in which severe congenital anomalies resulted in the combination of cloaca and female pseudohermaphrodism. The authors quote Dorland's Medical Dictionary in defining a cloaca as "an opening at the posterior end of the body of a vertebrate into which the intestinal, urinary and reproductive ducts open." The findings of laparotomy in one case and autopsy in the other demonstrated that a cloaca as defined did in fact exist along with ambiguity of the genitalia constituting hermaphrodism. There is a review of previously reported cases of cloaca (4) and nonadrenal female pseudohermaphrodism (4).

Comment: Techniques and knowledge now available allow a systematic approach to the determination of the basic defect in an infant found to have ambiguous genitalia. The first step in investigation is to determine the chromosomal sex pattern. When this has been demonstrated to be female, the most likely diagnosis remains virilizing adrenal hyperplasia, which can, of course, be established by study of the 17-ketosteroid excretion. Second most likely is the possibility that the female infant may have been masculinized in utero by hormonal therapy given the mother during pregnancy. Female pseudohermaphrodism not explained by either of the foregoing is extremely rare and may fall into the group represented by the cases reported in this article; namely, ambiguous genitalia associated with severe anomalies of the gastrointestinal and urinary tracts, usually including imperforate anus and fistulous communications between the tracts. Finally, one should not forget the rare possibility that the infant with ambiguous genitalia and female chromosomal sex pattern may represent true hermaphrodism, since the majority of such patients studied have shown a female pattern of chromatin distribution.

Acute Poisoning Associated with Inhalation of Mercury Vapor: Report of Four Cases. On the afternoon of Feb. 28, 1957, a 19-year-old mother of three children painted a space-heater in her two-room home with a mixture containing mercurcy, turpentine, and aluminum paint. In an attempt to make the paint "stick," the gas in this heater was lit and allowed to burn all night in the room where the mother and children were sleeping. During the night, the children were restless and seemed to have respiratory difficulty, and the mother experienced malaise, abdominal pain, diarrhea, shortness of breath, and cough.

On the following day, since the symptoms persisted, the family was treated in a clinic for upper respiratory infection with diarrhea. During the following night, all four had continuing respiratory difficulty, and at 8 a. m. the following morning, the 20-month-old girl died. The remainder of the family was then hospitalized and the body of this child brought for autopsy.

Approximately 30 hours after admission, the second child, a 30-month-old boy, died after having shown findings of a severe pneumonitis and eventually pneumothorax. The third child, a 4-month-old girl, also exhibited signs and symptoms of pneumonitis and pneumothorax, and died after four days, despite vigorous therapy, including BAL during the last two days of life. The mother similarly developed a severe pneumonitis but survived and made an apparently complete recovery. The outstanding findings at autopsy in the three fatal cases were those of erosive bronchitis, bronchiolitis, and severe interstitial pneumonitis. Minor changes were also found in kidneys and liver.

The circumstances surrounding this situation leave little doubt that these patients were victims of acute mercury intoxication by inhalation. The literature regarding this form of intoxication is reviewed and a discussion of diagnosis and therapy included.

Comment: This situation as described is striking in its tragedy and draws attention to the vexing problem of accident prevention. In this same issue of *Pediatrics* is a report entitled "Recent Trends in Accident Prevention," which describes the activities of the American Academy of Pediatrics in this field.

The Treatment of Allergy with Extract of Toxicodendron Quercifolia: A Controlled Series.—In a double-blind study, a comparison of effects upon various allergic disorders was made between an extract of Toxicodendron quercifolia (Anergex R_x) and a placebo (saline). Of 30 children given the extract, 14 were markedly improved, 6 practically improved, and 10 were not improved. The placebo was given to 26 children, and of these 7 were markedly improved, 9 partially improved, and 10 were not improved. In other words, 66% of patients in both groups were considered to show definite improvement. Therefore, no advantage of the drug over the placebo could be demonstrated in this study.

Comment: As pointed out by the authors, the most significant result of this study is the remarkable response of these allergic children to treatment, regardless of its nature. Marked and even dramatic improvement was noted in both groups, and the authors report their "embarrassing experience of having patients wire us from far off places for vials of salt-water 'boosters.'" Any investigator or other physician becoming enthusiastic about the therapeutic effects of any agent in the treatment of disease, particularly ones as variable as allergic disorders, would do well to read the results of this study and its discussion.

The Development of Prematurely Born Children with Birth Weights of Minimal Postnatal Weights of 1,000 Grams or Less.—This report is part of a long-range study of the progress of premature infants discharged from the Premature Nursery of the New York Hospital. From 1940 until 1952, 116 infants of birth weight less than 1,000 gm. or babies whose weights dropped below this level were considered eligible for study, this consideration being that they had reached an age of at least 4 years. Of these, 73 children were brought back for extensive study, including medical histories, social evaluation, physical examination and psychometric testing. Forty-three of the gorup did not return, and only the available information regarding eye defects and mentality could be presented. The following results were evident from the study of 73 children:

1. Physical health was usually good, with less illness apparently than might be encountered in a similar group of children not prematurely born. There was no increased tendency to respiratory or other disease.

2. Achievement of height within 1 S. D. of Iowa grid was widely varied from 1 to 12 years, with the majority of children reaching this level at 3 to 4 years of age.

3. There was a high incidence of eye defects, particularly strabismus and myopia.

4. Intelligence quotients ranged from 59 to 142, with an average of 94. Thirty-four measurements were controlled by comparison with the I. Q. of a sibling, and on the whole the premature fell significantly below the sib in this regard. Of these 73 studies 12 had I. Q.'s below 80; it is of considerable significance that of the 43 patients who were not studied 19 were known to be mentally retarded and 5 were in mental institutions. The authors point out the apparent increased risk of mental impairment in the very small premature. Of the various factors studied, including birth weight, sex, race, socioeconomic status and maternal complications, the only significant correlation of the I. Q. was with socioeconomic status.

Comment: This is an interesting and important study. The statistical analysis of the results of group studied loses considerable importance, however, in view of the fact this group comprised only approximately 60% of the total number of infants involved.

Radiology, Syracuse, N. Y.
Abstracted by William E. Anspach, M.D.

71, No. 5 (Nov.) 1958

* Responses of the Developing Fetal Nervous System to Roentgen Irradiation. Robert Rugh.—p. 729.

71, No. 6 (Dec.) 1958

* The Significance of Postoperative Pneumoperitoneum in Infants and Children. John W. Hope and Harry R. Cramer.—p. 797.

* Operative Cholangiography in the Diagnosis of Prolonged Jaundice in Infants. John H. Harris Jr., A. Edward O'Hara, and C. Everett Koop.—p. 806.
* Fibrocystic Disease of the Pancreas: Roentgen Manifestations. Harvey White.—p. 816.
* Fluoroscopy in Pediatric Radiology and the Implications of Image Intensification. John A. Kirkpatrick Jr.—p. 823.

Responses of the Developing Fetal Nervous System to Roentgen Irradiation.—The embryo and the fetus together represent the most dynamic period in the life of any organism, during which there is a constantly changing mosaic of developmental activity. In addition there is accelerating growth from the relative simplicity of the single-celled zygote to the multimillion-cell organism. Any insult to any part, or to the whole, during this phase may result in abnormalities which cannot be produced at any subsequent period in the life of the organism.

Ionizing radiations constitute a very powerful means of interfering with any biological process, and their effects are more marked and even of different kinds when the embryo or fetus is exposed than in postnatal stages—exaggerated because of the high radiosensitivity during any developmental activity and different because there is interference with organogeny. Developmental abnormalities can be produced by irradiation only during the prenatal stages.

In the fetus there is no uniformity in the reaction from moment to moment, owing to the constantly changing structures and dynamic activity. It is therefore impossible to predict, on any quantitative basis, the teratogenic effect of any exposure to ionizing radiations. This unpredictability is not to be confused with normal radiological variability, which is probably primarily of genetic origin, but rather to be attributed to other factors peculiar to prenatal development. Certain abnormalities are more likely to occur after even low-level irradiation at specified periods of development; yet it is possible to produce some of the same changes at later stages but only by higher levels of irradiation.

The nervous system integrates and permeates every part of the organism; from about the 20th day in the human embryo, and continuously until some weeks after birth, there are embryonic differentiating neuroblasts in increasing abundance, developing from their neurectodermal precursors in association with each of the various organ systems. Neuroblasts are the intermediate stage between the primary precursor and the ultimate neuron and are now believed to be the most radiosensitive of all cells, rarely surviving an exposure of 40 r. The nature and the extent of radiation damage to the embryo or fetus will be somewhat commensurate with the number and distribution of such radiosensitive neuroblasts present at the moment of irradiation. The ability of the developing organism to reconstitute itself after such an insult will depend somewhat upon the number and distribution of the remaining less sensitive precursors of the neuroblasts. Microcephaly, probably the most frequent sequela of fetal irradiation, varies in degree in different individuals, partly in relation to the abundance of undamaged neuroblast precursors. The resilience of the embryo following irradiation may result in a topographically normal but quantitatively reduced organism, particularly deficient in neural elements. After x-irradiation the resultant organism will be deficient particularly in neural elements, but the functional consequences of this deficiency will depend upon the stage of development and on the degree of insult. Because of these factors, the x-irradiation of the human embryo or fetus should be discouraged, particularly during the first trimester.

The Significance of Postoperative Pneumoperitoneum in Infants and Children.—To evaluate postoperative pneumoperitoneum, the abdomen in infants was examined roentgenographically 24 hours after a laparotomy. The authors were surprised to find the absence of air in the peritoneal cavity in all infants. Later the postoperative examination was reduced to a film taken in the recovery room within 30 minutes after surgery. In only 3 of a group of 19 was there any air in the peritoneal cavity and in each of these cases air was not visualized at 24 hours. These observations were in marked contrast to those in adults following laparotomy, where it was generally agreed that air in the peritoneal cavity may persist up to 14 days. The authors conclude that if more than a trace of air is present for more than 24 hours after a laparotomy, a perforated viscus is the most probable cause in children of 8 years or younger.

Operative Cholangiography in the Diagnosis of Prolonged Jaundice in Infants.—Surgery of the biliary passages, which is frequently difficult in adults, is more difficult in children because of the size of the ducts. If the biliary tree can be shown to be normal, exploration

is not justified. On the other hand, it is of definite value to the surgeon if the site and nature of an atresia can be demonstrated prior to exploration of the hepatoduodenal ligament.

The peritoneal cavity is entered through a small but subcostal incision, and the gallbladder is identified. Its appearance frequently gives a clue to the underlying pathology. If it is of normal size and contains normal-appearing bile, a patent communication between the gallbladder and the liver may be assumed, but this in no way reflects the caliber of the communication. Furthermore, this does not aid in the differentiation between the "inspissated bile syndrome," viral hepatitis, and atresia of the common bile duct. A mushroom catheter is inserted into the gallbladder through a small cholecystostomy, and held in place with a pursestring suture. After irrigation of the biliary ductal system with saline to eliminate artefacts caused by bile plugs, 8 to 20 cc. of 15% Urokon is injected through the catheter. The actual amount of the contrast material used is dependent upon the size of the gallbladder. The x-ray exposure is made after approximately 80% to 85% of the contrast medium has been introduced. If there is roentgen evidence of atresia of the ductal system, the initial incision is extended to allow adequate exposure for exploration of the porta of the liver.

Operative cholangiography has been employed in 12 instances at The Children's Hospital of Philadelphia. Three children were 1 month of age and the oldest was 21 months, and the average age was 8 months. Of the 12 patients, 6 were found to have normal extrahepatic ductal systems, 1 had atresia of the common bile duct, and 4 had congenital atresia of the hepatic ducts. In all but one instance, operative cholangiography correctly demonstrated the state of the biliary ductal system prior to exploration of the hepatoduodenal ligament.

The authors conclude that only early surgical correction can prevent the cirrhotic process in suitable cases and that it is of great importance to have early exploration and study of the biliary ductal system by operative cholangiography.

Fibrocystic Disease of the Pancreas: Roentgen Manifestations.—Fibrocystic disease of the pancreas is a hereditary, generalized, glandular disease of children manifested by pancreatic deficiency, chronic pulmonary lesions, disturbances of the sweat and salivary excretion, and cirrhosis of the liver. Involvement may be multiple or single.

This disease is limited almost entirely to the Caucasian race; rarely found in Negroes and never in Mongolians. The name suggests a primary disease of the pancreas, but this is misleading, since almost all of the exocrine glands are involved. However, fibrosis of the pancreas is an outstanding pathologic finding. In the United States there are approximately 7,000 cases out of 4,200,000 live births.

The deficiency of pancreatic enyzmes and alteration of the mucoprotein in the duodenal secretion result in an abnormal thick, tenacious meconium in the newborn, and 10% of the babies with this condition will have acute intestinal obstruction. The clinical manifestations are chronic diarrhea, foul fatty stools, and general impairment of nutrition.

Ninety per cent of the deaths in fibrocystic disease are the result of chronic pulmonary involvement—the earlier the disease makes its appearance, the poorer the prognosis. The degree of intrabronchial obstruction, extent and control of the superimposed Staphylococcus aureus infection, and the fibrosis of the lung have a definite relationship in this respect. From this underlying pathologic picture the radiologist can expect to see pneumonitis, atelectasis, emphysema, bronchiectasis, and fibrosis.

The absolute diagnosis is made by the demonstration of a total or partial enzymatic deficiency in the duodenal secretions or an elevated sodium (over 80 mEq/liter) and chloride (over 60 mEq/liter) in the sweat. Fingerprints on an agar plate of silver nitrate and potassium chromate show prominent prints when the sweat electrolytes are at a high level.

Ten per cent of these children developed intestinal obstruction. Many other conditions causing difficulty in making the diagnosis are ruled out by characteristic symptoms and signs and a negative sweat test.

Intensive antibiotic therapy and surgery will undoubtedly prolong life, so that we will see these children reaching their teens and young adult years, with chronic pulmonary disease.

Roentgen manifestations are limited principally to the chest and abdomen.

Fluoroscopy in Pediatric Radiology and the Implications of Image Intensification.—Recognition of the value of fluoroscopy in pediatric radiology implies not only an appreciation of the functional manifestations of disease but also of the possibilities for teaching and for research which are inherent in the method. Therefore, a device that produces a fluoro-

scopic image 1,000 times brighter than that of the conventional screen, with significantly lower exposure to the patient, must be considered a major radiologic advance.

Acute inflammatory disease of the lungs in an infant may be first manifested by obstructive emphysema, which is difficult or impossible to recognize on radiographic study. Early in life emphysema may be the only manifestation of cystic fibrosis of the pancreas. Disturbances in aeration of the lungs, which are best recognized fluoroscopically, often accompany congenital lesions of the tracheobronchial tree, of the pulmonary parenchyma, and of the heart and great vessels, e. g., congenital lobar emphysema, congenital adenomatoid malformations of the lungs, and vascular rings. Fluoroscopic observation in order to determine the size and nature of pulsation of the major vessels, the character of the intrapulmonary vasculature, and the configuration of the heart, is an integral part of the radiologic approach to congenital heart disease. Evaluation of the esophageal activity in the infant who regurgitates may reveal a functional basis for such regurgitation. Under certain circumstances the diagnosis of pyloric stenosis and intussusception may be established by means of fluoroscopy and the diagnosis of aganglionic megacolon follows careful fluoroscopic study.

The brighter fluoroscopic screen allows for safer clinical fluoroscopy and cinefluorography. Fluoroscopic examination is made with the lights on, at 0.5-1.0 ma. and 60-70 kv., depending on the size of the patient. Dark adaptation is not necessary, and the levels of brightness are such that cone vision is utilized. A lighted room makes for a much more cooperative child, so that fluoroscopic time is decreased and the examination is rendered more accurate and definitive.

Zeitschrift für Kinderheilkunde, Berlin

Abstracted by Gunnar B. Stickler, M.D.

81, No. 5 (Oct.) 1958

Age Dependent Differences in the Sensitivity of Human Erythrocytes to Lipopolysaccharides from E. Coli. O. H. Braun, P. Bock, and O. Lüderitz.—p. 503.

The Psychological Situation of Juvenile Thiefs and Its Projection in the Scenotest. G. Biermann.—p. 509.

* The Method of Calcium Balances in Young Infants. W. Häusgen.—p. 529.

Acute Keratoconus in Mongolism. S. Wilde.—p. 550.

Postencephalitic Parkinsonism with Gazing Spells in a Child. E. Machetanz.—p. 555.

* Quantitative Diagnosis and Control of Therapy in Urinary Tract Infections. F. Linneweh.—p. 567.

Formation and Excretion of Proteolytic Enzymes of the Stomach in the Fetus and Newborn. H. Wagner.—p. 580.

Regarding the Diagnosis of Fibrocystic Disease of the Pancreas. B. S. Schultze-Jena.—p. 589.

Clinical and Serological Examinations in the Hemolytic Disease of the Newborn Due to ABO Incompatibility. D. Wöllner and H. Plückthun.—p. 609.

81, No. 6 (Nov.) 1958

* Catamnestic Examinations of Children with Encephalitis. J. Pietsch and I. Schindling.—p. 645.

Intubation of the Trachea and Artificial Respiration with Changing Pressures in Prematures with Respiratory Distress. U. Keuth.—p. 660.

* Transaminases and Glycolytic Enzymes in the Serum of Prematures. U. Stave.—p. 675.

The Importance of the Eye for the Postnatal Development of the Regulation Centers for Water Metabolism. H. Rodeck.—p. 683.

The Vascular Factor in Blood Dyscrasias and Its Treatment. F. Linneweh.—p. 706.

The Congenital Rhabdomyosarcoma of the Bladder. M. Habedank.—p. 717.

Bornholm Disease. A. Windorfer and H. H. Schricker.—p. 733.

Fecal Lysozyme Excretion in Infantile Enteritis. O. H. Braun.—p. 742.

Examination of the Circulation at Rest According to Wexler-Böger in Patient with "Drop"-like Hearts. W. Angel.—p. 752.

Dysplasia Renofaciales in Anchipodia. F. Fritzsche.—p. 760.

Quantitative Diagnosis and Control of Therapy in Urinary Tract Infections.—The fact that urinary tract infections are often overlooked in infants is reemphasized. The inadequacy of urine sedimentation for the diagnosis of leukocyturia is pointed out, and an extensive comparison shows that leukocyte counts of the unsedimentated urine in counting chambers are of greater significance. The author also favored quantitative bacteriologic analysis of the urine. Bacterial counts in the urine were used to demonstrate that skin infections due to Staphylococcus pyogenes are frequently associated with elevated staphylococcal counts in the urine (*Ztschr. Kinderh.* 81:200, 1958).

Use of the method of quantitative urinalysis raises the question in my mind of whether the author is not overdiagnosing urinary tract infections.

The Method of Calcium Balances in Young Infants.—This paper should be valuable to anyone interested in balance determinations in infants. It contains a detailed discussion of available methods and a critical review of the extensive literature. The author proved convincingly, with examples, that the usual three-day metabolic periods are misleading, at least as far as calcium balances are concerned. He described in great detail his own method and presents general rules for balance determinations in infants.

Catamnestic Examinations of Children with Encephalitis.—The authors attempted to reexamine a group of children who had had encephalitis. Unfortunately, they failed to define their criteria for the original diagnosis of encephalitis and they did not state the time interval between original disease and follow-up examination.

The purpose of the study was to determine the amount and degree of residuals among various types of encephalitis. However, it is my opinion that a study of this type amplifies rather than lessens our lack of knowledge regarding the extent of involvement of the central nervous system in the course of various common viral diseases in children. In the first place, we often do not know the virus responsible for the primary illness, nor do we know the extent of involvement of the central nervous system during the acute disease. Studies like the one presented by the authors also fail to rule out disease of the central nervous system preceding an acute viral disease. Only carefully planned prospective studies may ultimately allow us to know more in regard to the prognosis of viral diseases with involvement of the central nervous system, and even this type of study would have to be done in patients in whom disease of the central nervous system was excluded during preceding repeated routine examinations.

Transaminases and Glycolytic Enzymes in the Serum of Prematures.—The author found the values for serum GOT, GPT, and aldolase and lactic acid dehydrogenase among 54 prematures within the range of normal values of full-term infants. However, he found the mean values of the transaminases lower and those of the glycolytic enzymes higher than in newborns.

No correlation to bilirubin values was found.

News and Comment

ANNOUNCEMENTS

Care of Premature Infants.—In the fall of 1959, the Institutes for Physicians and Nurses in the Care of Premature Infants at the New York Hospital-Cornell Medical Center, under the sponsorship of the New York State Department of Health and the United States Children's Bureau, will begin their eleventh year of operation. These institutes are designed to meet the needs of physicians and nurses in charge of hospital premature nurseries and special premature centers, and of medical and nursing directors and consultants in state and local premature programs. The attendance at each Institute is limited to six physician-nurse teams. The program for physicians is of two weeks' duration and that for nurses of four weeks' duration. Participants pay no tuition fee, and stipends are provided to help cover expenses during attendance at the Institute. Institutes for the 1959-1960 year are definitely scheduled to start on the following dates: Sept. 21, 1959; Nov. 2, 1959; Jan. 4, 1960; Feb. 8, 1960, and May 9, 1960.

Early application for these institutes is essential since plans are contingent on the number of applications received. Additional information may be secured by writing Box 143, Institute in the Care of Premature Infants, New York Hospital, 525 E. 68th St., New York 21.

New Research Director Announced.—Dr. Arild E. Hansen, Professor and Chairman of the Department of Pediatrics, University of Texas Medical School (Galveston), has been appointed research director at Children's Hospital of the East Bay, Dr. James L. Dennis, medical director, has announced.

Dr. Hansen will succeed Dr. Irvine McQuarrie, who will continue as research consultant.

Dr. Hansen will assume his duties in midsummer.

Pediatric Fellowships.—The Department of Pediatrics of the University of Colorado Medical Center announces the availability in 1960 and 1961 of Pediatric Fellowships in Allergy, Infectious Disease, Hematology, and Premature and Newborn Nursery. Applicants should be graduates of approved schools of medicine and should have completed at least one or more years of hospital training. Preference will be given to those who are in the course of completing the pediatric hospital training. Preference will be given to those who are in the course of completing the pediatric hospital training required for the examination of the American Board of Pediatrics. The fellowships, for one or two years, include fundamental laboratory research and clinical investigation, as well as training in clinical diagnosis and management.

Inquiries should be sent to Henry K. Silver, M.D., University of Colorado Medical Center, 4200 E. Ninth Ave., Denver 20.

Adoption of Children.—The American Academy of Pediatrics has recently published a 64-page manual on Adoption of Children. Copies of this manual can be purchased from the American Academy of Pediatrics, 1801 Hinman Ave., Evanston, Ill., for $1.00.

This manual has been prepared by the Committee on Adoptions under the chairmanship of Dr. Samuel Karelitz, aided by consultants from the Children's Bureau, the Child Welfare League of America, and the International Social Service. It emphasizes the role of the physician, especially the pediatrician, in the adoptive process. His responsibility to the child being considered for adoption, to the natural parents, the adoptive parents, and the community are all considered. Special sections deal with current trends in the adoption of handicapped children, with the problem of intercountry adoption, and the physician's relation to the law. Of special note is an extensive bibliography on many phases of the adoption process which will be of interest to workers in many fields involved in adoption.

American Heart Association Fellowships.—Public contributions to the annual Heart Fund campaign provide the funds for Association-supported research. Support is given not only to studies with a direct bearing on problems of cardiovascular medicine but also to basic research in a wide range of scientific disciplines. The Association recently announced its national awards for the 1959-1960 fiscal year, representing an allocation of approximately $3,300,000.

Following are brief accounts of the categories in which applications may be made:

Established Investigatorships.—Awarded for periods of up to five years, subject to annual review, in amounts ranging from $6,500 to $8,500 yearly plus dependency allowances, to scientists of proved ability who have developed in their research careers to the point where they are independent investigators. In addition, a grant of $500 is made to the investigator's department. Applicants for Established Investigatorships may apply for grants-in-aid to support their research at the same time they apply for Established Investigatorships. Applications must be received before Sept. 15, 1959.

Advanced Research Fellowships.—Awarded for periods of one or two years to postdoctoral applicants who have had some research training and experience but who are not clearly qualified to conduct their own independent research. During the second year of tenure they will be permitted to spend up to 25% of their time in professional and scientific activties not strictly of a research nature, provided that these will contribute to their professional development and do not involve services for a fee. These stipends range from $4,600 to $6,500 annually. Additionally, a grant of $500 is made to the investigator's department, as in the case of Established Investigators. Applications must be received by Sept. 15, 1959.

Research Fellowships.—A limited number of awards are available to young men and women with doctoral degrees for periods of one or two years to enable them to train as investigators under experienced supervision. Annual stipends range from $3,800 to $5,700. Applications must be received by Sept. 15, 1959.

Grants-in-Aid.—Made to experienced investigators to help underwrite the costs of specified projects, such as equipment, technical assistance, and supplies. Applications must be received by Nov. 1, 1959.

Further information and application forms may be obtained from the Assistant Medical Director for Research, American Heart Association, 44 E. 23d St., New York 10.

Louisiana Chapter, American Academy of Pediatrics.—The Louisiana Chapter of the American Academy of Pediatrics will present a fall scientific session under the sponsorship of Lederle Laboratories. The Baton Rouge Pediatric Society will act as host. The meeting will be held Friday, Sept. 18, 1959, at the Capitol House, Baton Rouge. The theme of the seminar will be Malignancies in Childhood and will include the following subjects and speakers:

1. Common Childhood Tumors: Dr. James Arey, Pathologist, St. Christopher's Hospital, Temple University, Philadelphia
2. Malignancies of the Endocrine System: Dr. Robert Greenblatt, Professor of Endocrinology, Medical College of Georgia
3. Abdominal Masses in Children: Dr. H. William Clatworthy Jr., Head, Division of Pediatric Surgery, Ohio State University
4. Radiologic Diagnoses of Childhood Malignancies: Dr. Frederic Silverman, Department of Radiology, Children's Hospital, Cincinnati
5. Advances in Treatment of Blood Dyscrasias: Dr. Wolf Zuelzer, Director, Child Research Center, Michigan
6. Chemotherapy of Malignancies: Dr. John Heller, Head, National Cancer Institute, Bethesda, Md.

In addition there will be two round tables with Dr. James King, St. Louis University, as moderator. At the noon banquet, Dr. John Young, Clinical Professor of Pediatrics, Southern University, will speak on Emotional Problems of Parents and Children.

There will be other week-end activities in Baton Rouge, on Saturday, Sept. 19, 1959:

1. Breakfast meeting of the Lousiana Chapter of the American Academy of Pediatrics
2. Sixth District Medical Society meeting, Saturday morning, with the following program:
   The Acute Abdomen in Infants and Children: Dr. H. Clatworthy
   Gonadal Dysgenesis: Dr. Robert Greenblatt
   Unrecognized Skeletal Trauma in Infants and Children: Dr. F. Silverman
3. Louisiana State University: Rice football game, Saturday afternoon

There will be no registration fees for the seminars. Wives are invited.

Those interested in attending are urged to make their own reservations, since there will be no Housing Bureau. Those desiring football tickets should write directly to the Athletic Department, Lousiana State University.

For any additional information, write Dr. F. M. Harris Jr., Secretary-Treasurer, 1401 N. Foster Drive, Baton Rouge 6, La.

Research Training Program.—Applications for Research Traineeships to begin before Sept. 1, 1960, are now being accepted by the Research Training Program of the Department of Pediatrics, University of Washington School of Medicine, Seattle. The program is limited to graduates with the M.D. degree, who are interested in a full-time academic career of research and teaching. Traineeships, supported by the National Institutes of Health, are, for a minimum of two years, subject to annual review. Stipends conform to the levels announced by the National Institutes of Health for postdoctorate fellows. The program for each trainee will be planned and supervised in cooperation with a committee of scientists and will consist of didactic courses in the physical and biological sciences as well as supervised research training in the laboratories of the Department of Pediatrics. Research work will be generally concerned with the biochemical aspects of intermediary metabolism and cellular differentiation. Persons interested in the program may obtain additional information and application forms by writing to the program director: Bruce Mackler, M.D., Department of Pediatrics, University of Washington School of Medicine, Seattle 5.

GENERAL NEWS

Specialists Certified by the American Board of Pediatrics.—The following candidates were certified as specialists by the American Board of Pediatrics, Inc., in Philadelphia, May 2, 3, and 4, 1959.

Alvarez-Pagan, Milton, San Juan, Puerto Rico.
Aronson, Natalie, University City, Mo.
Avery, Mary Ellen, Boston.
Berman, Donald R., Lowell, Mass.
Blake, Arnold, Longmeadow, Mass.
Bongiorno, Joseph R., Brooklyn.
Browne, Marie J., New Haven, Conn.
Claps, Albina Angela, New York.
Colgan, Margaret Thomson, Rochester, N. Y.
Cook, Thomas Edwin, Lake Jackson, Texas
Cramblett, Henry Gaylord, Iowa City.
Cunningham, Peter Ritsher, Guilford, Conn.
Curtis, Charles Pelham Jr., Southport, Conn.
Decker, Elisabeth Burnett, New York.
Donnellan, Elaine K., Boston.
Ducharme, Jacques-Raymond, Yonkers, N. Y.
Ellison, Richard T. Jr., Jenkintown, Pa.
Faigle, John F. Jr., Stony Brook, N. Y.
Fernald, Willard Barker, Columbus, Ohio.
Finck, Jerome, H., Detroit.
Fisher, John Apfel, Philadelphia.
Frawley, Stephen M., Brookline, Mass.
Gair, David R., Miami, Fla.
Gasparik, Mary Zonger, New York.
Gavis, Gustave, Monticello, N. Y.
Greenman, George Wallen, New Haven, Conn.
Guss, Louis, Norwich, Conn.
Gyves, William S., Brooklyn.
Hill, Louis Leighton, Cleveland.
Jansa, Milos A., Landover Hills, Md.
Kaplan, Seymour H., Great Neck, N. Y.
Kesim, Mufit Husam, Lakeland, Ky.
Kontras, Stella B., Columbus, Ohio.
Lerner, Herbert Irving, Chicago.
Lerner, Ruth Geyer, Chicago.
Luke, Mary Jane, Charlottesville, Va.
Macfarlane, Noble T. Jr., Lexington, Ky.
Mahaney, Thomas P., Saginaw, Mich.
Mansmann, Herbert C. Jr., Pittsburgh.
McGovern, Murray G., Ontario, Canada.
McLean, William T. Jr., Philadelphia.
Mellman, William J., Philadelphia.
Mitchell, Fred Neal, Charlotte, N. C.
Notterman, Rebecca F., Hightstown, N. J.
Omans, Walter B., Philadelphia.
Pfaff, Mary Louise, Briarcliff Manor, N. Y.
Salomone, Michael E., Staten Island, N. Y.
Sandberg, Anna, Providence, R. I.
Selby, Samuel, Yellow Springs, Ohio.
Sherry, Samuel Norman, Cambridge, Mass.
Sitarz, Anneliese L., Summit, N. J.
Smid, Arthur Charles, Naperville, Ill.
Stuart, James D., Elmhurst, Ill.
Taylor, Irwin Thomas, Fort Worth, Texas.
Tuke, Charles T., Rochester, N. Y.
Wagner, Harold H., Hicksville, N. Y.
Walton, Robert Owen, Cleveland.
Weinstein, Norman, Fairfield, Conn.
Weymann, Donald Richard, Smithtown, N. Y.
Yablin, Bernard A., Syracuse, N. Y.
Zager, Ruth Priscilla, Philadelphia.

Special Foreign Certificate

Tang, James Shi-chow, New York.

Books

BOOK REVIEWS

Annual Review of Medicine: Volume 9. Edited by David A. Rytand, M.D., and William P. Creger, M.D. Price, $7. Pp. 530, Annual Reviews, Inc., Grant Ave., Palo Alto, Calif., 1958.

This is the ninth volume of the *Review*, and like its predecessors it remains an excellent authoritative survey of medical progress in many diversified fields of medicine. Each of the 28 chapters is edited by distinguished men in their respective fields who attempt to briefly review appropriate publications on the subject covering the interval since the last *Review* to July, 1957

The wealth of articles analyzed precludes the editors from writing more than a few sentences relating the article to the general topic being reviewed. For example, the section on cancer by Charles Gordon Zubrod, M. D., is covered in 10 pages and quite clearly and concisely covers recent studies of neoplastic diseases. However, in order to bring out the highlights of progress in the entire field of cancer, Dr. Zubrod reviews 220 publications, which necessitates limiting the amount of comment for each article.

The editorial evaluations of the progress in the different medical fields make this review much more than just an index book; but certainly the chief use of the volume will be made by those with an interest in obtaining a comprehensive review of recent publications in a given field of medicine.

SAMUEL T. GIAMMONA

L'Asthme dans l'enfance. By H. Jumon, Ancien interne des Hopitaux de Paris. Price, 900 fr. Pp. 122, with 2 figures. Masson & Cie, 120 boulevard Saint-Germain, Paris 6e, 1958.

This brief book in French on the clinical features and therapy of asthma in infants and children is written by a practitioner for practitioners. It is largely based on his personal experience. The bibliography consists of 17 references exclusively from the French literature. No attempt is made to deal comprehensively with the subject matter from the international point of view. The clinical portion consists of a rather elaborate classification of different types of asthma, with their prognosis. This is the most detailed part of the book, and the one in which the author's approach and that of the American School would be most in accord. The section on therapy is primarily of interest in pointing up the differences in rationale for therapy and in recalling, what to us, are almost historic forms of treatment. These include hot applications to chest and neck, hot foot baths, cupping, bleeding, sterile abscess for non-specific response, treatment of dehydration with hypertonic glucose or sucrose solutions, and the injection of serum from Type O donors. The author also uses antibiotics, theophylline, on occasion sympathicomimetic drugs, corticotropin (ACTH), and corticosteroids for acute asthma. He mentions only two of the latter, delta-cortisone and delta-hydrocortisone.

The most interesting phase of treatment, which differs from our own practice, is the stress placed on "Spa" treatment of asthma. The regimen at La Bourboule, Le Mont-Dore, Saint-Honoré-les-Bains, are described in detail. The waters at these places all contain arsenic, and other minerals, and have some degree of radioactivity. They are used for aerosols, bathing, etc.

This book would be of interest to allergists who are curious about a French approach to asthma. It is not recommended to any who are not thoroughly familiar with the background of the various types of treatment for asthma. It seems to the reviewer that the author makes little distinction between proved and unproved remedies. Certain of his clinical statements could be challenged, such as "One does not encounter retarded children among them" (asthmatics).

SUSAN C. DEES

Outline of Orthopaedics. Second Edition. By John Crawford Adams. Price, $8. Pp. 428. E. & S. Livingstone, Ltd., 16 and 17 Teviot Place, Edinburgh 1; The Williams & Wilkins Company, 428 E. Preston St., Baltimore 2, 1958.

The second (present) edition of this well-conceived book is pleasing in its conciseness of presentation. Mr. Adams has very skillfully covered a wide variety of orthopedic conditions briefly, and has presented a conservative, modern approach to the problems of diagnosis and treatment.

The discussion of primary tumors of bone is, of necessity, brief, but the reader nevertheless has the distinct impression that oversimplification has arisen. The definition of osteogenic sarcoma as a tumor arising from primitive bone-forming cells is clear, but is at variance other concepts of osteogenic sarcoma in which the tumor, by definition, is required to form neoplastic bone.

Lichtenstein in 1953 related eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease under the heading of "histiocytosis X." This should have been included in the discussion of lipoid granulomatosis.

Regional orthopedics is dealt with in an orderly manner; it covers causative and pathologic aspects, clinical features and treatment. Preceding each section in this part of the volume, pertinent features of examination and special anatomic considerations are reviewed.

Illustrations are excellent and well placed. The index is complete and easy to use. The book is of convenient size and has an attractive cover, which tended to warp slightly in the copy of the reviewer.

This book should prove extremely valuable for use by students and others in occasional contact with orthopedics.

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1. Edsall, G.; Altman, J. S., and Gasper, A. J.: Am. J. Pub. Health, 44: 1537, 1954.

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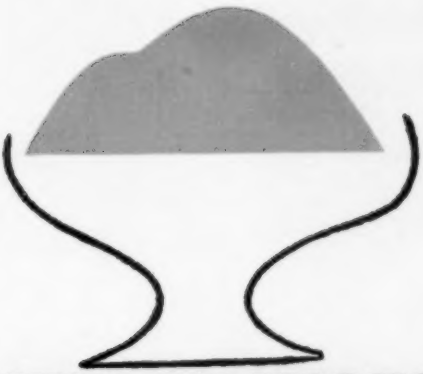

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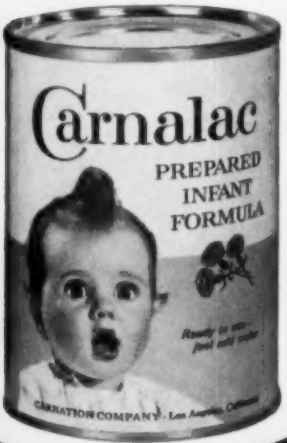

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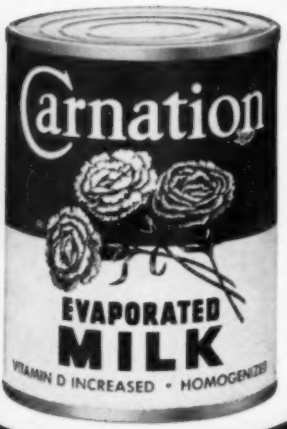

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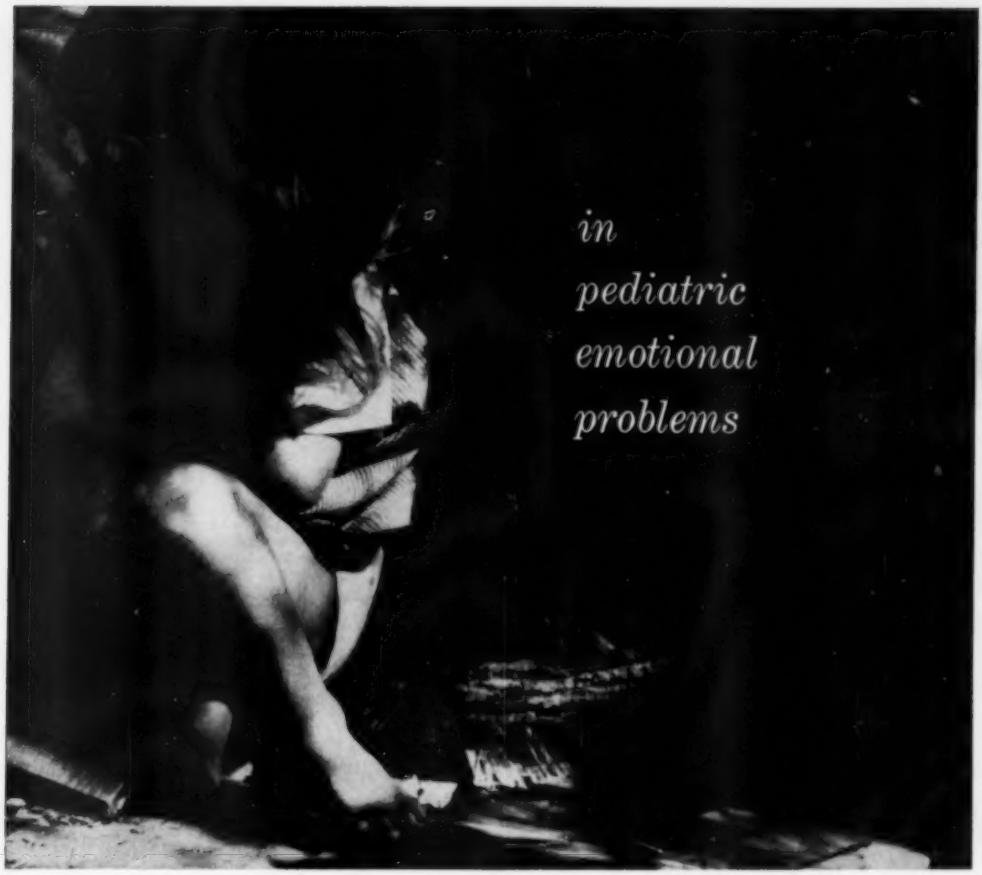

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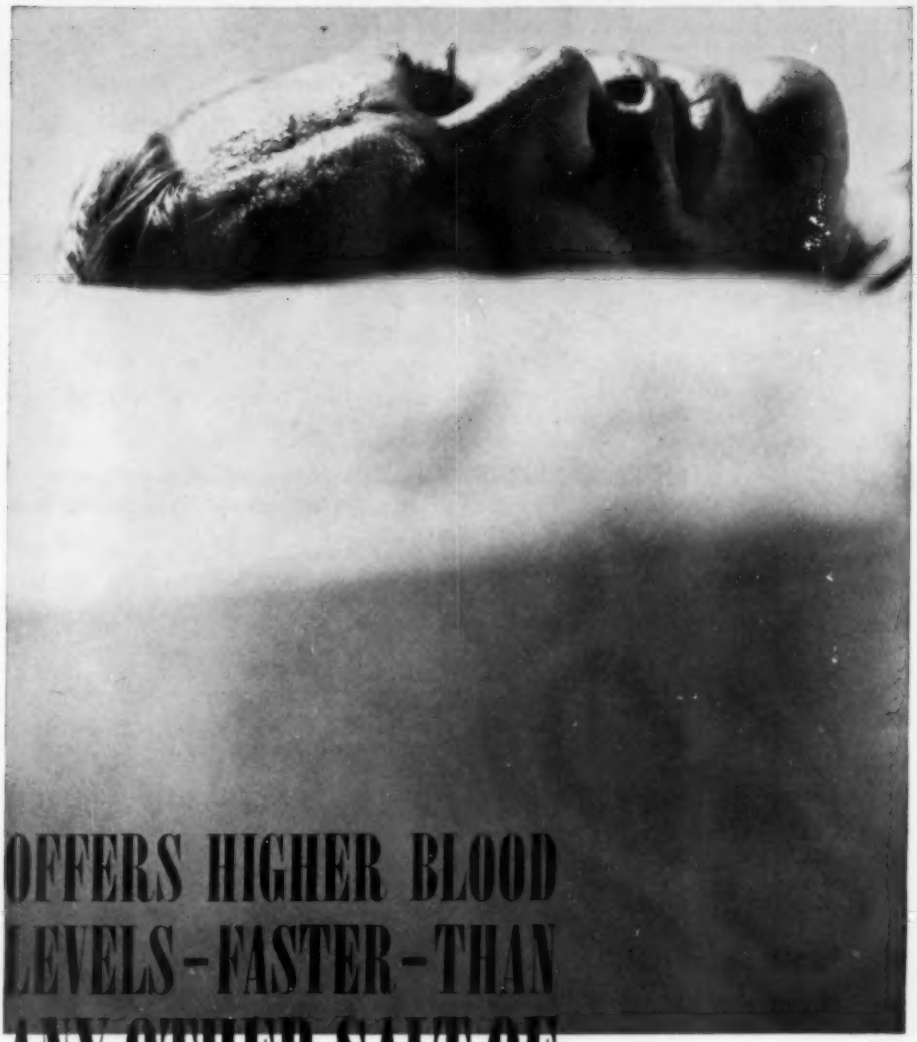

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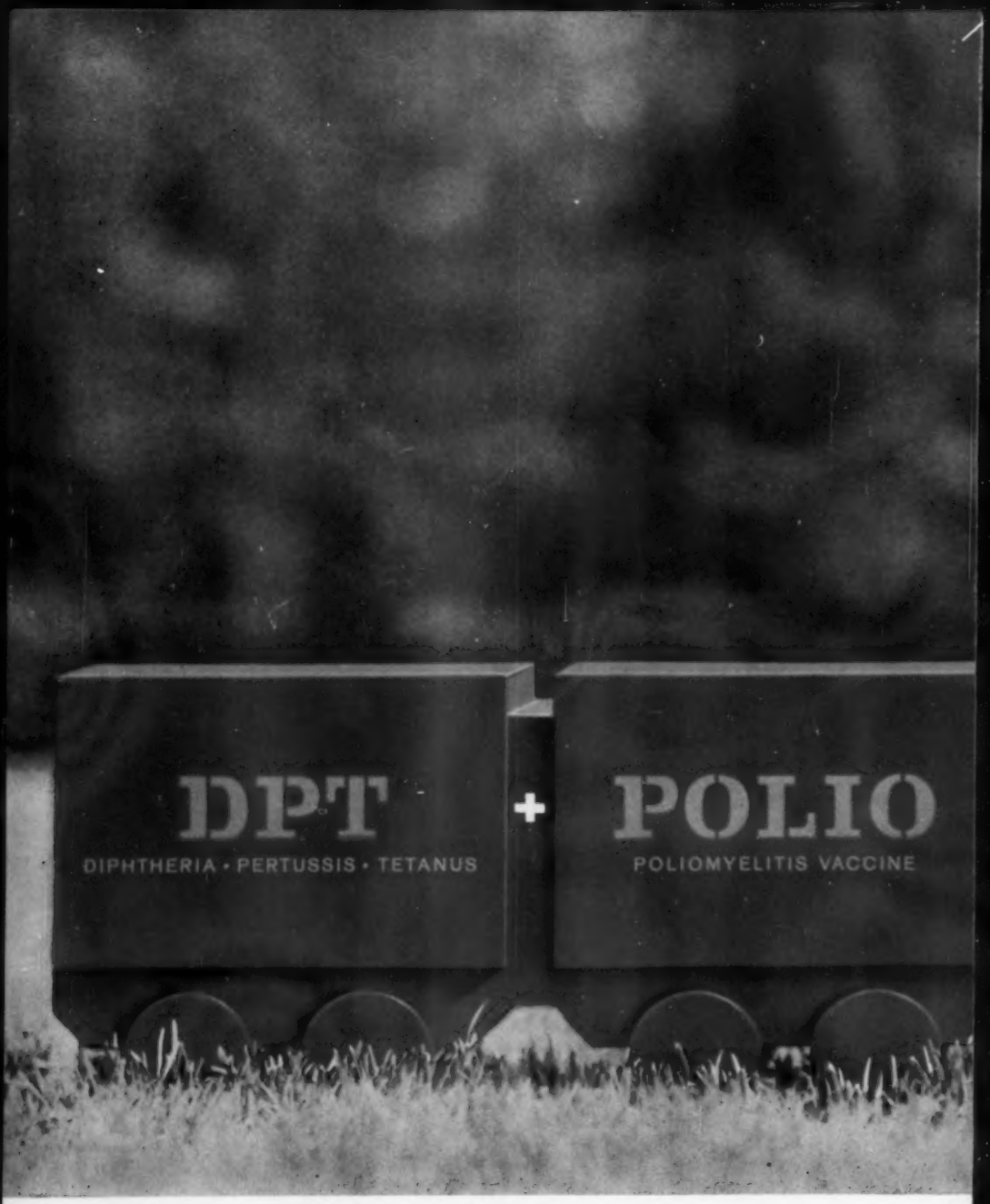

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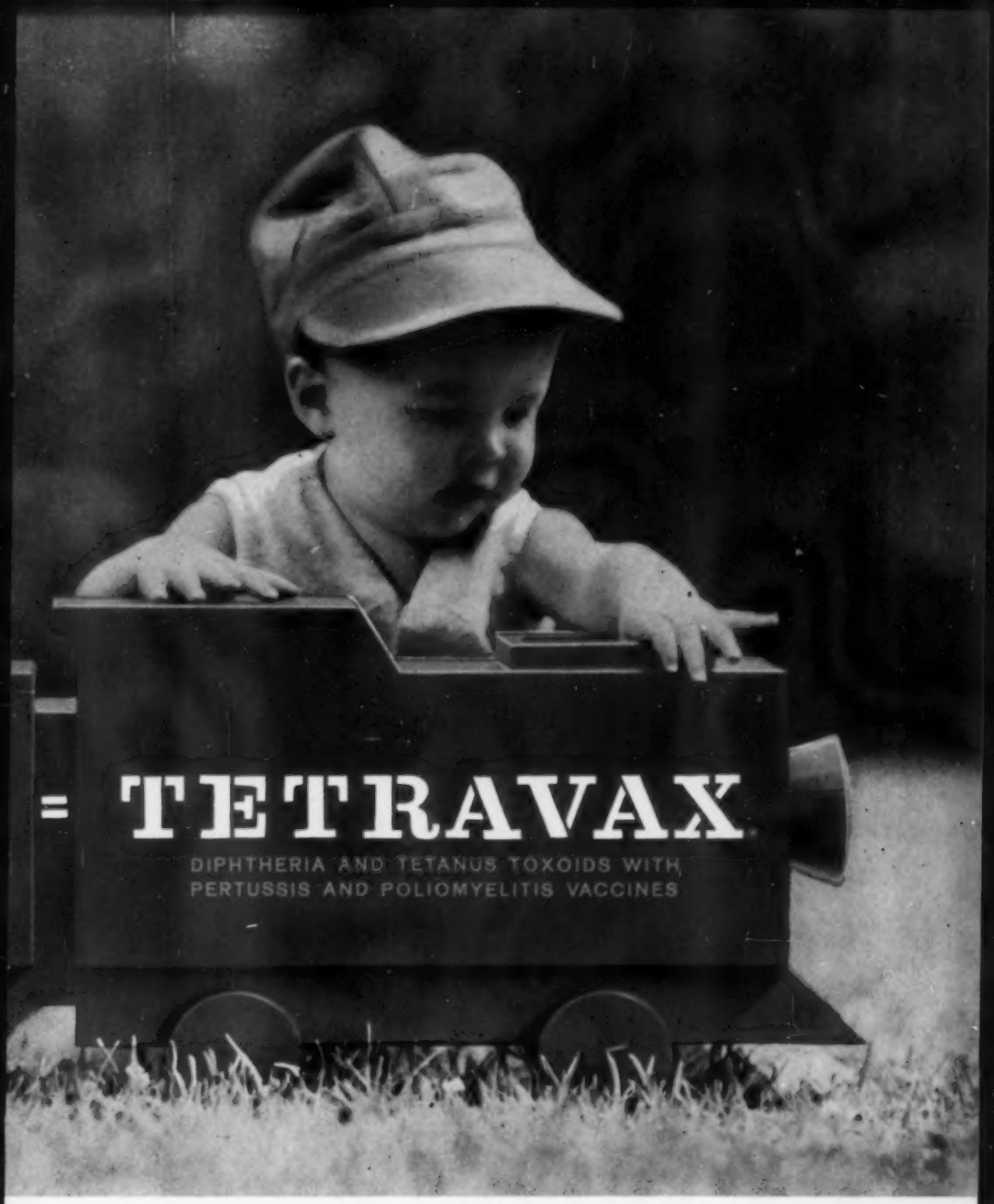
against 4 diseases:

Poliomyelitis — Diphtheria — Pertussis — Tetanus



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"Paremycin (tincture of opium and neomycin sulfate in combination) provided prompt relief of hyperperistalsis and other intestinal discomfort with rapid, lasting pathogenic control."[1]

- The first and only combination of neomycin sulfate and tincture of opium—and in optimum ratio.
- Rapid clinical control—after only 1-4 doses and within 12 hours.
- Convenient small doses—only ½—2 teaspoonfuls q.i.d. in infants and children.
- Delicious banana flavor—clear, non-chalky, non-bulky.

SUPPLIED: Bottles of 6 and 3 fl. oz.

CITED REFERENCE:
1. Schneider, A. J.: The Symptomatic Relief of Pediatric Gastrointestinal Disturbances with Paremycin (To be submitted for publication).

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Brand of Neomycin Sulfate and Tincture of Opium **ELIXIR**

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1 mg. (2 drops) to 1.5 mg. (3 drops) per Kg. (2.2 lb.) of body weight.

Each teaspoon (5 cc.) of Elixir Demerol = 50 mg. Demerol HCl
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Each drop of Elixir Demerol = 0.5 mg. Demerol HCl

Supplied: Elixir Demerol, 50 mg. per teaspoon (5 cc.), bottles of 16 fl. oz.
Subject to regulations of the Federal Bureau of Narcotics.

1. Junkin, C. I.: *Canad. Anaesthetists' Soc. J.* 3:208, July, 1956.
2. Glaser, Jerome: *J. M. A. Georgia* 45:514, Dec., 1956.

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